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HENRY PHIPPS INSTITUTE

FOR THE STUDY, TREATMENT, AND
PREVENTION OF TUBERCULOSIS

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FOR THE STUDY, TREATMENT, AND
PREVENTION OF TUBERCULOSIS

PRINTED FOR THE
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* Since September 1st, 1919, the Dispensary has been conducted by the State Department of Health.

† Since December, 1919, the Hospital has been conducted by the Eagleville Sanatorium for Consumptives.

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PULMONARY TUBERCULOSIS AND CONDITIONS SIMULATING IT

A CLINICAL LECTURE GIVEN AT THE HENRY PHIPPS INSTITUTE, APRIL 10, 1918

By H. R. M. LANDIS, M.D.
Philadelphia

This morning I wish to discuss with you the various conditions which may be, and frequently are, mistaken for tuberculosis. There are those who believe that a diagnosis of tuberculosis should be arrived at by exclusion; that is, that a tuberculous infection is to be acknowledged only after you have satisfied yourself that the symptoms and physical signs are due to that cause and no other. On the other hand, there are those who reverse this process of reasoning and hold the opinion that in the event of tuberculosis being suspected you should hold the tubercle bacillus accountable for the manifestations of illness presented by the patient until you definitely prove that some other pathologic process is accountable. Personally I belong to the last-mentioned group. In the first place, pulmonary tuberculosis is by far the most frequent disease of the chest which you will encounter. The mathematical chances, therefore, are always in favor of such a diagnosis in any individual who presents any of the symptoms commonly associated with tuberculosis. In the second place, the failure to keep in mind the seriousness of a failure in diagnosis leads many to mistake tuberculosis for a benign and harmless affection, such as bronchitis.

Ignoring or forgetting these facts is responsible for many cases being overlooked or mistaken for other conditions. The term "protean" has been applied to many other diseases, but of no condition is it so true as tuberculosis. A tuberculous infection of the lungs may ape any disease to which the thoracic viscera are subject, no matter whether it be acute or chronic.

To establish a diagnosis of tuberculosis you are to take into account the history, the location and nature of the pathologic changes, and, finally, the laboratory tests.

1. *The History.*—(*a*) Does this show that the patient has been

exposed to infection with the tubercle bacillus either by reason of contact with a member of his family or through his associates in his place of employment? (*b*) Does the history reveal the occurrence of illness in the past which may be considered as reasonably certain to be an evidence of tuberculous infection? There are three symptoms, for instance, the occurrence of which is overwhelmingly in favor of a diagnosis of tuberculosis. First, the history of an hæmoptysis. Now, while it is true that blood-spitting can and does occur in a variety of conditions, it is to be looked upon as an evidence of tuberculous infection of the lungs until it can be definitely proved to be otherwise. The occurrence of idiopathic blood-spitting in the temperate zones, therefore, is to be regarded as tuberculous in origin in the vast majority of cases. Secondly, a history of pleurisy with or without an effusion. At the very lowest estimate fully 85 per cent. of all cases of pleurisy are to be regarded as being tuberculous in origin. Insurance companies have for some years recognized the importance of this condition. Their statistics show that of applicants giving a history of having had an attack of pleurisy, four times as many will eventually die of tuberculosis as compared to those without such a history. Thirdly, the occurrence of a fistula in ano is to be regarded as strong presumptive evidence of a latent tuberculous infection of the lungs. It is stated by many that fully 85 per cent. of these fistulæ are tuberculous in nature. A history of such a condition is considered by some insurance companies as a cause for rejection.

These three manifestations—hæmoptysis, pleurisy, and fistula in ano—are often prodromal symptoms and may antedate definite tuberculous changes in the lungs by years.

A history of lobar pneumonia and typhoid fever is quite common among tuberculous patients. Our experience in the Phipps Institute is as follows: Of 4466 patients, 17.77 per cent. stated that they had had pneumonia; of 5895 patients, 1083, or 18.3 per cent., stated that they have had typhoid fever. Recognizing the fact that tuberculosis is one of the most protean of all diseases and that it frequently manifests itself in an acute form, either under the guise of an attack of lobar pneumonia or of typhoid fever, it is a fair assumption that not a few of the cases just alluded to were of that nature. When it is stated that there have been two or three attacks of pneumonia or typhoid fever, or further questioning shows these attacks to be

atypical, the suspicion is strong that the real trouble has been an acute exacerbation of tuberculosis which has spontaneously subsided.

Finally, the history of the present illness is of the greatest importance. The principal symptoms of tuberculosis are cough with or without expectoration, malaise, digestive disturbances, loss in weight, hæmoptysis or blood-streaked sputum, chest pain or distinct pleuritic pain, and slight afternoon fever. All of these symptoms, in the beginning, rarely occur in the same patient. In one malaise will be the predominant feature; in another, the cough; in still another, digestive disturbances will dominate the picture. None of them are pathognomonic of the disease. They become relatively important or unimportant only when taken in consideration with other facts in the history and the physical signs.

2. *Pathological Anatomy.*—No one can hope to achieve any degree of success in any branch of medicine without a definite conception of the pathologic changes involved in the various diseases under examination. Lack of knowledge in this respect is responsible for most of the errors in connection with diseases of the chest. Not only is tuberculosis often overlooked because of failure to take into account the morbid anatomy of the disease, but still more often it is mistaken for other conditions. A tuberculous infection of the lungs as it occurs in adults always first manifests itself at one or the other apex. The initial deposit is a small cluster of tubercles located about one and one-half inches from the apex. From this point the disease has a tendency to spread backward and always downward. Depending on the stage of the invasion—that is, whether the disease is moderately advanced or far advanced—the physical signs will always show the evidence of the greater destruction of lung tissue at the point where the disease first appeared; namely, at the apex. Thus there will be the signs of dense infiltration at the summit of the lung, and as the base is approached the signs will be correspondingly less marked. In advanced cases signs of a cavity at one or the other apex or at both apices is almost the rule.

Keeping in mind the "line of march" of the disease is essential if one is to distinguish between tuberculosis and a number of conditions which, although presenting the same symptoms, have an entirely different pathology.

3. *Laboratory Aids.*—The most important of these aids is the

examination of the sputum. This procedure is so simple that it can be done by any one. It is essential, however, to bear in mind certain facts. In the first place, there are several varieties of the streptothrix group which are extremely resistant to acid and are not decolorized by Gabbet's stain or 20 per cent. sulphuric acid. Any organism which resists 30 per cent. nitric acid can be looked upon as certainly being the tubercle bacillus. In the minds of many there still lingers a misapprehension as to the significance of sputum examinations. You not infrequently hear physicians state that the sputum had been examined once and, as tubercle bacilli had not been found, they did not consider that tuberculosis was present. It is to be borne in mind that one negative examination means nothing, no matter what the stage of the disease may be. If you have under consideration a case in the very early stage of the disease, not only one but a dozen sputum examinations may be negative without your being able to say the disease does not exist. Early closed cases often do not show the presence of tubercle bacilli in the sputum. Another mistake in regard to the interpretation of sputum examinations is the failure to heed a number of negative reports when the symptoms and physical signs clearly indicate gross and extensive change in the lungs. In such instances it is far too often taken for granted that tuberculosis is undoubtedly present, in spite of the negative results, and no thought is entertained of other etiologic factors. Again, in cases of the type just mentioned the physician too often takes for granted that the tubercle bacillus is the cause of the trouble and the sputum is not examined at all.

Tuberculin tests were at one time resorted to in order to determine the presence or absence of tuberculosis, especially in doubtful cases. For this purpose the subcutaneous injection of tuberculin may be resorted to occasionally. Its routine use is not to be encouraged, and there are some who condemn this method entirely on the ground that it not infrequently arouses into activity a latent and inactive process which may cause serious trouble. The Von Pirquet and Morro tests, which were so universally used a few years ago, are gradually passing into disuse. They are indicative of hypersensitiveness to the tubercle bacillus or its products and, except in children under two years of age, do not distinguish between clinical tuberculosis and healed or quiescent foci.

The *complement-fixation test* has been used to distinguish between cases in which the tuberculous process is active, or about to become so, and those which are healed and which may be disregarded. Its reliability has not yet been determined.

Within the past few years the X-*rays* have been lauded as the only sure and reliable method of determining the presence of tuberculosis and also of distinguishing the disease from other affections of the lungs which may simulate it. If one is to believe what the ultra-enthusiastic röntgenologists claim, it is a waste of time to spend our efforts in trying to find out the cause of the trouble by the usual methods of physical diagnosis. Baetjer put the matter very succinctly when he stated that the only point at issue is an etiologic diagnosis in the early stages of the disease. As he has pointed out, this is not possible by means of the X-rays, as a number of other conditions give rise to changes in the lungs and bronchi which are not to be distinguished from tuberculosis. By the time the X-ray picture is definitely that of tuberculosis the clinical evidence is so clearly apparent that the need of an X-ray examination is superfluous. My own experience is that in the vast majority of cases the time-honored clinical methods are efficient; in a relatively few the X-rays will detect changes which have escaped the clinician and, on the other hand, a few will escape the röntgenologist which are detected by the clinician. Within the past few months I have knowledge of three cases in which an experienced röntgenologist reported negatively as to the presence of tuberculosis when all three of the cases showed the presence of tubercle bacilli in the sputum.

Acute Bronchitis.—Cough is the most frequent, and often in the beginning the only, symptom of an early tuberculosis. Attributing a cough of this nature to an attack of acute bronchitis is one of the most frequent errors made. This is largely due to the slight and indefinite physical signs which are often elicited in the early stages of tuberculosis. In the absence of anything definite the cough is assumed to be negligible and probably an evidence of acute bronchitis or trachitis. A safe rule to follow in such cases is to consider a cough which has lasted for six weeks or longer, and for which there is no adequate explanation, as being strong presumptive evidence of a beginning tuberculosis. The longer such a cough has been present the more suspicious one should be that it is not due to a simple

benign bronchitis. The latter, in the vast majority of cases, has a duration of three or four weeks; rarely does an acute bronchitis become subacute and continue indefinitely. The young man I am about to show you has been a victim of such a mistake. Six months ago he developed a cough, for which he consulted a physician after it had been present six weeks. He was told that he had bronchitis, and was treated, until two weeks ago, for this condition. During this time the cough has steadily become worse and the sputum more and more profuse, in spite of the use of various cough remedies. On several occasions the sputum was blood streaked. In addition, he gradually lost twelve pounds in weight and suffered from an increasing malaise. Recently he developed slight huskiness of the voice. In spite of assurances that the condition was nothing more than a bronchitis, he himself became apprehensive that all was not well, and on his own suggestion his sputum was examined and found to contain many tubercle bacilli. Examination of his chest shows distinct diminution of motion down to the fourth rib on the left side, and over the greater part of the left upper lobe the breath sounds are suppressed, and after cough showers of fine crackling râles are heard. The disease has now progressed to a point where recovery is doubtful; the best that can be hoped for is an arrest of the process and a limited sphere of activity for him the rest of his life. You may think this is an exaggerated instance. So it is, but none the less it is one that is encountered with considerable frequency.

You will note and bear in mind the two cardinal mistakes in this case: First, that of regarding as simple bronchitis a cough which had persisted for months; and, second, the failure to examine the sputum at the very onset of the trouble.

Chronic Bronchitis.—This condition is not often primary. In the great majority of instances it is secondary to some other condition. It is commonly encountered in those past the middle period of life who are asthmatic or emphysematous. Among those who suffer from emphysema a chronic winter cough is common. During the summer months the cough is very slight or it may disappear entirely. Overlooking a tuberculous infection and mistaking it for chronic bronchitis usually occurs in one of two ways. In the first place, it is often assumed that a cough which has persisted for months must be due to a chronic bronchial condition. In the second place, when such

a condition actually is present, there is a failure to realize that a tuberculous infection is also present. In this latter group the emphysema often marks the physical signs of the tuberculous process. Furthermore, the constitutional signs in these cases are often slight and do not attract the attention of either the patient or the physician. Again, there are not a few cases of tuberculosis which pursue a latent course and in which there are considerable fibroid changes in the lungs. In such cases there may be scattered râles throughout both lungs. This fact, taken in conjunction with a chronic cough and little or no failure in the general health, leads the unwary to overlook the possibility of the serious lesion and look upon the process as a chronic bronchitis. While in the majority of these cases the experienced physical diagnostician is not deceived, an error can be avoided by every one if the sputum is examined. Indeed, it should be a fixed rule to do this in all cases of chronic cough, no matter how slight the chances are that a tuberculous infection may be present.

Bronchiectasis.—An extremely common error is the mistaking of bronchiectasis for tuberculosis. Dilatation of the bronchi occurs in practically all instances in which extensive fibrosis of the lungs has taken place. It occurs in its most characteristic form in the massive type of fibrosis where an entire lobe or even one entire lung has undergone fibroid changes. The etiology is varied. Any condition which causes inflammatory changes in the pulmonary tissue may gradually produce a fibrosis and, later, dilatation of the bronchi. Tuberculosis itself is a frequent cause of both fibroid changes in the lungs and dilatation of the bronchi, but in these cases the bronchiectasis is not usually so marked as in the cases of non-tuberculous fibrosis. Dilatation of the bronchi is more commonly encountered at the base of the lungs than at the apices. It is to be borne in mind, however, that the condition does occur at the apices more often than is usually thought.

The usual text-book description of bronchiectasis is that the condition is characterized by the expectoration of large quantities of sputum which often is of an extremely foul odor. This emptying of the bronchi takes place two or three times a day, and during the rest of the time there may be little or no expectoration whatever. Out of a very considerable number of cases of bronchiectasis which I have seen the expectoration of very large quantities of very foul sputum is

the exception rather than the rule. In the majority of cases the sputum, while profuse, is not always foul, nor does it come up in very large quantities at infrequent intervals.

The symptoms of bronchiectasis are cough, expectoration, blood-streaked sputum, or small hæmoptyses. The cough may be paroxysmal and attended with profuse expectoration. Owing to the associated fibrosis there may be some shortness of breath. Constitutional symptoms are usually absent in spite of the foul secretions in the bronchi.

In the case I now show you the most noticeable feature on inspection and the one that attracts our attention at once is the extreme clubbing of the fingers and the curving of the nails over the ends of the fingers, the so-called "parrot-beaked" finger-nails. Whenever you see clubbing of this type you can be almost positive that you have to deal with extensive fibrosis of the lungs and an associated bronchiectasis. Extreme clubbing is sometimes seen in cases of empyema; it is also a constant feature in congenital heart-disease, but in this condition the ends of the fingers are also cyanosed. While clubbing of the fingers is very frequently seen in tuberculosis, it is rarely of the extreme type encountered in cases of non-tuberculosis fibrosis of the lungs.

Next to the extreme clubbing of the fingers, it is to be borne in mind that the abnormal physical signs, as in the present case, are commonly confined to the base of one or the other lung. This fact is almost proof positive that the condition is not tuberculous. The man I now have before you has been under observation for nearly twelve years; his sputum is negative for tubercle bacilli, and the physical signs consist of limitation of motion at the right base, distant breath sounds, mixed râles, and the signs of a cavity near the angle of the scapula. The latter condition is commonly present in these cases and is due to dilatation of the bronchi at the root of the lung. At the present time I have two such cases under my care at the White Haven Sanatorium, both being sent in under the belief that they had tuberculosis.

One word more as to this condition: I have already referred to the dilatation of the bronchi being limited to one or the other apex of the lung. In such cases the symptoms and physical signs (especially that of cavity) are identical with those encountered in tuberculosis. Clubbing of the fingers in this type is absent, probably because the drainage is good and the secretions do not stagnate in the bronchi.

Examination of the sputum is the only certain means of distinguishing apical bronchiectasis from tuberculosis. If the sputum is repeatedly negative for tubercle bacilli a diagnosis of fibrosis of the lung and dilatation of the bronchi is permissible.

Pneumoconiosis.—Closely allied to the above condition is pneumoconiosis. Although this condition is described in all the text-books, it rarely is referred to in our daily work. A diagnosis of pneumoconiosis is hardly ever used in either the morbidity or mortality returns. The secondary changes which are caused by the inhalation of inorganic dust are the ones usually referred to, such as chronic bronchitis, emphysema, asthma, etc. Now that more and more interest is being taken in industrial diseases the term pneumoconiosis as indicative of a distinct pathologic process will probably be more and more used.

The condition arises under the following circumstances: If a worker is exposed to inorganic dust (notably that containing much silicia) for a period of years the fine dust particles are carried into the respiratory tract and gradually set up a chronic inflammatory condition. This eventually leads to extensive bilateral fibroid changes constituting a fibrosis of the lungs. It is important to know that after the condition of pneumoconiosis becomes well established the changes are more noticeable in the right lung than the left, and that, furthermore, the changes are often more pronounced about the hilus and the apices. To one who is unfamiliar with the fact, both physical signs and an increase in the shadows of the X-ray plate, more marked at the apices, might be interpreted as being due to tuberculosis. When the process has reached an advanced stage both lungs are markedly scarred and the physical signs are indicative of gross pathologic changes. Pneumoconiosis may lead to extensive fibroid changes which later has added to the picture a tuberculous infection. The mistake is often made of calling pneumoconiosis tuberculosis because of the similarity of symptoms and the physical signs. It is not possible to differentiate the two except by examination of the sputum. The presence or absence of tubercle bacilli will be the determining point.

This condition serves to emphasize the importance of knowing the occupation of the patient. Whenever it is stated that the occupation is that of a potter, a coal miner, a metal grinder, or, in fact,

any employment in which inorganic dust is a factor, the diagnosis of pneumoconiosis should at once suggest itself.

Malignant disease may involve the lungs primarily or secondarily, and may be either carcinomatous or sarcomatous in nature. Among other types of malignant disease which affect the lungs or pleura may be mentioned endothelioma, and secondarily hypernephroma, and malignant deciduoma.

Primary malignant growths of the lung are rare and the diagnosis is not easy. It is usually made by exclusion. These cases have a cough, some expectoration, blood-tinged sputum, they emaciate and lose strength, and usually have an irregular type of fever. Occasionally the sputum is markedly hemorrhagic and presents the appearance of currant jelly. When present, sputum of this kind is extremely suggestive of malignant disease. Dyspnœa is often a marked feature and is out of all proportion to the amount of damage in the lungs as demonstrated by the physical signs. In a case seen here in the Institute several years ago extreme dyspnœa was about the only symptom present. The physical signs consisted of nothing more than the presence of a few râles scattered throughout both lungs. At the autopsy not more than four or five nodules, about the size of a walnut, were found in each lung. The primary growth in this case was a small unrecognized scirrhous cancer in the left breast.

Primary malignant tumors occur by preference about the root of the lung or at the bases—a valuable point in the differential diagnosis. They may, however, be limited entirely to an upper lobe. The sputum should be repeatedly examined in order to definitely rule out the presence of tubercle bacilli. Recently several excellent röntgenologic studies have been made of malignant disease of the lungs and these have shown that the X-ray picture is quite characteristic of the condition. All doubtful cases should be subjected to such an examination.

Secondary or metastatic malignant disease of the lungs is not uncommon and, as a rule, is easily recognized. Any individual who has had a malignant growth removed or who is known to have such a growth should be suspected of having a metastasis of the lungs, if respiratory symptoms develop.

Malignant disease of the lungs is overlooked far too frequently, and in every instance the error is to be attributed either to the fact

that the sputum is not examined or that the warning of repeated negative examinations is not heeded. Given a patient who is obviously going down hill, who has marked respiratory symptoms, and in whom the physical signs are indicative of gross pathologic changes in the lungs, some other explanation of the trouble must be sought for if the sputum, after at least half a dozen examinations, fails to show the presence of tubercle bacilli. That the mistake is a common one is attested to by the fact that institutions devoted to the care of tuberculosis patients are constantly having sent to them individuals who really have malignant disease. Thus in one institution a recent report shows that out of 198 autopsies on supposedly tuberculous individuals five proved to be due to malignant tumors of the lungs.

Lobar Pneumonia.—It is not sufficiently recognized that, while tuberculosis, as a rule, is characterized by an insidious outset, it very often begins abruptly and simulates one of the acute infectious diseases. This is particularly true of lobar pneumonia. Not infrequently tuberculosis will first manifest itself with a chill or chilly sensations, pain in the side, cough, bloody expectoration, and a high continuous type of fever. Such an onset is identical with that of pneumonia, and for a week or ten days the two conditions are not to be differentiated clinically. Furthermore, there will be the signs of partial or complete consolidation. It is worth remembering, however, that it is the apex or upper lobe which is always the site of the abnormal signs if the condition is tuberculous; if due to croupous pneumonia, the apex may be involved, but the base of one or the other lung is the common site. In such cases no suspicion is entertained that the condition is other than a croupous pneumonia until ten days or two weeks have elapsed, when, if the condition is tuberculous, the temperature begins to fluctuate, crisis does not occur, sweating is apt to take place, and the sputum becomes purulent. Examination of the sputum will now show tubercle bacilli to be abundantly present. It may take several weeks to determine the question, however, if the pneumonia occurs in an individual who already has tuberculosis, because in these cases a rapid spread of the tuberculosis may be attended with symptoms similar to those just mentioned.

The process is to be suspected as being tuberculous from the very beginning in all cases of apical involvement if there is a family history of tuberculosis or if the individual gives a history of having

been in ill-health for some time, or if he has had a slight hacking cough for several months. It is frequently stated by patients that they have never been well since they had an attack of pneumonia some months previously, or the physician states that the tuberculosis developed as a result of the pneumonia. For some reason, hard to explain, it has long been known that when a true lobar pneumonia does occur in a definitely tuberculous patient it has little or no effect on the tuberculosis. Therefore one can usually be pretty certain that when it is said pneumonia caused the tuberculosis such is not the case, but the trouble was tuberculous from the very beginning.

Syphilis.—There are many who refuse to accept a diagnosis of syphilis of the lung or, at any rate, believe that it is encountered only very rarely. Since the discovery of the *Spirochæta pallida* and the Wassermann reaction, especially the latter, more and more reports are appearing on the subject of pulmonary syphilis. Personally I am of the belief that the condition occurs with greater frequency than is at present believed.

The diagnosis is always a matter of excluding all conditions which may account for the symptoms presented except syphilis. Without going into the subject exhaustively, I will relate the facts in one case and show you another. These cases are among some eight or nine observed here at the Institute of what we believe to be syphilis of the lung. Several years ago we had under observation a married woman of thirty-three years of age who applied for treatment because of a cough of some months' duration, yellowish expectoration which was blood tinged on several occasions, loss in weight, and slight, irregular fever. Abnormal physical signs were present at the right apex. The diagnosis seemed to be evident, although tubercle bacilli were not found. This was accounted for because of the slight amount of pulmonary involvement, the assumption being that the lesion was a closed one. She attended the dispensary regularly, but at the end of eight months her condition was unchanged. Finally, about this time she complained of severe nocturnal headache. We then noted, what we had previously disregarded, that her history stated that she had had three miscarriages—a fact that should have aroused our suspicions from the beginning. A Wassermann test proved to be strongly positive. Two doses of salvarsan, followed by mercury and

iodide of potassium, led to a disappearance of the fever, a gain in weight, and a rapid subsidence of the cough.

The man I now show you is, as you see, apparently in robust health. When first seen, two years ago, he had not been able to work for four or five months. He had lost a great deal of weight, had a slight afternoon fever, a cough and expectoration, which was blood tinged at times. In addition, he felt very weak. Examination of his chest showed that there was some diminution of expansion, slight impairment of the percussion note, feeble breath sounds, and fine râles at the right apex. Owing to the fact that he gave a clear history of a luetic infection eighteen years previously, a Wasermann test was made and found to be strongly positive. His sputum was negative for tubercle bacilli. We therefore considered him to be suffering from syphilis and not tuberculosis. Salvarsan, followed by mixed treatment, caused a disappearance of the symptoms and a gain in weight of about forty pounds. He has been back at work and perfectly well for about eighteen months. There can be no doubt that there are not a few individuals presenting symptoms such as these two patients have who are treated for tuberculosis when in reality the true nature of the trouble is a latent syphilis.

Syphilis is to be suspected in a woman who gives a history of several miscarriages, in a man if one or both testicles are hard and indurated, or in either in case of enlargement or tenderness of the sternal ends of the clavicles or ribs. These are among the commoner of the syphilitic stigmata. It is to be borne in mind that both syphilis and tuberculosis may exist in the same individual.

Mycotic Infections of the Lungs.—Infection of the lungs with some one of the yeasts or moulds may occur. Although the total number of such infection is not great, they should always be kept in mind in cases which present every evidence of tuberculosis but in which tubercle bacilli are persistently absent from the sputum. In such an event the sputum should be studied from the standpoint of other possible infecting organisms. Every now and then one is rewarded by the finding of one of these unusual infections. In the order of their frequency the following conditions may be encountered: streptothricosis, actinomycosis, blastomycosis, coccidiodal granuloma or California disease, aspergillosis, and sporotrichosis. All of these conditions are characterized by cough, mucopurulent and, at times,

blood-tinged sputum or small hæmoptyses, pain in the chest, loss of weight, and fever. While they may invade any portion of the lung, the infiltrated area is frequently limited to one apex, or, when first seen, a large portion of a lung may be uniformly invaded. Unless the lesion is localized at the base of the lung, there is nothing about these cases to indicate that they are other than tuberculous in character. The key to the situation is the examination of the sputum. If this is repeatedly negative for tubercle bacilli, another source of the trouble is to be sought for.

It may be worth while mentioning that several of these mycotic infections have a curiously restricted geographical distribution. The great majority of cases of systemic blastomycosis which have been reported in this country come from the immediate vicinity of Chicago. A single instance of this disease has been observed here in the Institute. Coccidiodal granuloma or California disease is restricted, apparently, to a single district—the San Joaquin Valley, in California. Of the forty cases so far recorded, all but one or two have occured in this area. Sporotrichosis, which usually manifests itself as a skin lesion, although the lungs are occasionally involved, has been observed in this country almost exclusively in the region comprising the Mississippi River basin; of 73 cases thus far reported, 68 have come from this locality. The majority of the cases of pulmonary aspergillosis have been observed in France. It has been noted among those who handle grain and in men engaged in the forcible feeding (mouth to beak) of pigeons. The others have a very wide distribution, especially the streptothrix group, which is by far the commonest of all.

Pulmonary Distomatosis.—This condition is also known as lung-fluke disease, parasitic hæmoptysis, and endemic hæmoptysis. It is deserving of mention, for, although the United States are not included in its geographical distribution, it may be encountered at any time in those who have resided in the Far East. The disease occurs endemically in Japan, China, Korea, and the Island of Formosa. The principal symptoms are chest pain, cough and blood-streaked sputum, or a frank hæmoptysis. The diagnosis rests on the absence of tubercle bacilli and the presence of the eggs of the worm in the sputum. The eggs are golden yellow in color and larger than the eggs of other parasites common to man. They may be seen with the unaided eye as brownish specks if a small portion of the sputum con-

taining them is pressed between a cover-slip and slide and held up to the light. As both tuberculosis and distomatosis may occur in the same individual, both conditions should be kept in mind in those who have lived in the endemic zone.

Mitral Stenosis.—At first sight it would not seem likely that a cardiac lesion would give rise to mistakes. In all institutions devoted to the care of tuberculous patients, however, it is not an uncommon occurrence to have sent to them cases of chronic heart-disease, particularly mitral stenosis, in the belief that tuberculosis is present. This is to be ascribed to the fact that such patients often have a cough, blood-tinged expectoration, shortness of breath, and often the characteristic pre-systolic murmur and thrill are not present. In addition, the sputum is either not examined or the significance of several negative examinations is not heeded. In this frozen section which you now see you will note that the lungs are unusually healthy in appearance and that the heart is greatly enlarged. This specimen was obtained from the anatomical department of the University of Pennsylvania. The cause of death, in this case, was given as pulmonary tuberculosis.

Thoracic Aneurism.—The signs of aneurism of the arch of the aorta, particularly the transverse and descending portions, are often obscure and pass unrecognized. Very often there will occur in such cases considerable chest pain, cough, and bloody expectoration. In addition patients suffering from aneurism are often somewhat emaciated and have a slight amount of fever. Furthermore, as the tumor may extend toward the apex or, because of compression on a main bronchus, cause a feeble respiratory murmur on one side, the signs, taken in association with the symptoms, lead to an erroneous diagnosis of tuberculosis. It is well to remember, however, that the two conditions are not uncommonly associated. So far as naeurism is concerned, the easiest way of determining its presence is by means of an X-ray examination. Patients complaining of vague but persistent substernal pain should always be subjected to such an examination.

In briefly considering these various conditions which bear, in some instances, a close resemblance to pulmonary tuberculosis, and in others only a superficial likeness, it has been my desire to point out the fact that in nearly every instance a mistake can be avoided if certain well-established rules are kept in mind. First, the examination of the sputum. This should never be neglected in any case in which tuber-

culosis is suspected. In the very early cases it is, as a rule, negative, but in those cases in which the presence of râles at the apex indicates the presence of moisture the sputum should be examined a sufficient number of times to make it reasonably certain that another cause of the trouble is to be sought for.

Where the signs and symptoms indicate the presence of a well-marked tuberculous lesion it should never be taken for granted that tuberculosis is, of necessity, the true diagnosis. It is because of neglect in such cases that many instances of bronchiectasis, pneumoconiosis, mycotic infections, malignant disease, and even cardiorenal disease are mistaken for tuberculosis. A single negative examination in a case with extensive pulmonary damage demands that the examination be repeated until tubercle bacilli are actually found or until a sufficient number of negative examinations make it clear that some other cause of the trouble must be thought of. Secondly, it is essential to keep in mind the morbid anatomy of tuberculosis. A lesion occurring in one of the upper lobes may or may not be tuberculous; one limited to the base of the lung is almost certainly not tuberculous. Finally, remember that, while there is no symptom which is pathognomonic of tuberculosis, the occurrence of an hæmoptysis or an attack of pleurisy or the presence of a fistula in ano is the strongest kind of evidence in favor of the trouble being tuberculous.

A ROENTGENOLOGICAL STUDY OF THE EFFECTS OF DUST INHALATION UPON THE LUNGS

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ROENTGENOLOGIC STUDY OF THE EFFECTS OF DUST INHALATION UPON THE LUNGS*

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'HE possible pathologic features and the various causes of increased thick-ess of the prominent linear shadows, pecially those extending from the hilus the base of so many individuals exam-ed for tuberculosis and other condi-ons, have been questions about which ore or less doubt has existed. Further-ore, it is frequently difficult to assign their exact diagnostic value, in the etection of early pulmonary tubercul-sis, the more isolated thickened trunk adows often found in the apical reg-ns. In attempting to derive a better nderstanding of the causes of these anges from normal appearances it was ecided to approach the subject by a udy of the chests of a large number of ndividuals engaged in various dusty ccupations. This work was instituted bout a year ago on a small scale, but soon proved to be of so much clinical nd roentgenologic interest that it has een continued throughout the past year s time could be spared.

As a rule, we have found firms and orporations quite willing to have the nvestigations carried out upon their mployees, and it has frequently been to heir advantage so to do, either by being ssured that the dust inhaled by their en was not so harmful as was claimed, r by having ways and means suggested hereby the dangers from dust inhala-tions could be lessened. The Trenton Potteries Company and the Whitehall Cement Works have been most generous in supplying material and otherwise aiding us. A number of carpet, plush and silk workers were furnished through the kindness of Dr. J. W. Schereschewsky, Surgeon U. S. Public Health Service, and the remainder has been supplied through the Occupational Clinic of the University Hospital. Up to the present time one hundred and thirty-seven individuals have been examined, distributed through the following occupations:

Organic dust	
Carpet and plush workers	18
Tobacco workers	13
Silk workers	1
Inorganic dust	
Potters	39
Metal grinders	20
Cement workers	20
Asbestos workers	15
Coal miners and marine firemen	10
Not classified	1
Total	137

Each case has had a throrough clinical examination, followed by a roentgenoscopic study and a roentgenographic examination by stereoscopic plates. The clinical and roentgenologic studies have

* Read at the Eighteenth Annual Meeting of the American Roentgen Ray Society, New York, September, 1917.

been made independently, and as this is in the nature of a preliminary report during the progress of our investigations, there has as yet been no comparison of the details brought out by the two methods of examination, except in a general way. It is obvious, therefore, that all minor details should be omitted from this report, and the results of our investigations at this time be limited to a statement of certain well established general facts.

The entire subject is naturally to be regarded as a study of pneumoconiosis, a general term employed in referring to the effects induced in lung structure by the prolonged inhalation of abnormal quantities of dust. In a general study of the subject we have preferred to omit all reference to such terms as anthracosis, siderosis and chalicosis for the reason that they are indicative of the results of inhalation of certain kinds of dust, whereas many occupations imply the breathing of various forms, and the effects are the same in general but may vary in degree.

This report deals entirely with the roentgenologic aspect of the subject and is made at this time in an endeavor to aid in the more accurate roentgen diagnosis of pulmonary disease. The clinical and pathologic aspects of pneumoconiosis are by no means new, but thorough roentgenologic studies have been very few. Perhaps the most valuable contribution is to be found in United States Health Bulletin No. 85, issued January 1917, comprising a clinical and roentgenologic study of 433 cases of "miners' consumption" among the zinc miners in Missouri, by Dr. A. J. Lanza, Surgeon

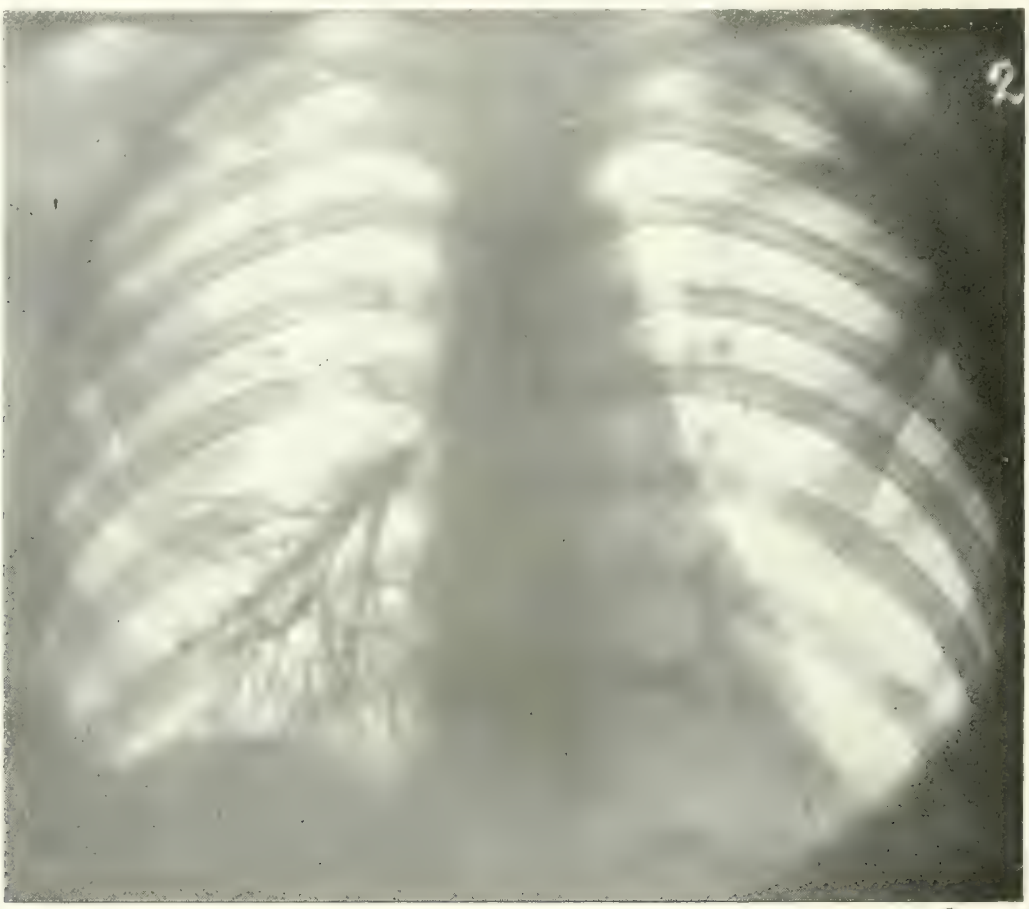

Fig. I. Outline of the Lower Portion of the Bronchial Tree by Bismuth.

Chest of a young girl with supposed esophageal stricture, but in whom the supposed obstruction was merely neurotic in origin. The bismuth meal passed directly into the trachea and most of it descended into the right bronchus. Note the distribution of the lower branches. Dust inhalation does not seem to affect the outermost ones.

Fig. 2. Pneumoconiosis in Metal Ball Grinder (Dry). Seventeen Years' Occupation.

The hilus shadows are greatly enlarged and linear markings are thickened, especially to the right base. There is intense mottling with small dense discrete spots on both sides, but more on the right.

Fig. 3. Pneumoconiosis in Potter. Forty Years' Occupation. Showing Comparatively Little Evidence of Dust Effects for This Time.

The hilus shadows are slightly increased, linear markings thickened, and there is a moderate amount of discrete mottling most marked around the middle of each lung.

of the U. S. Public Health Service, and Dr. Samuel B. Childs of Denver. Another important contribution was made by Dr. W. W. Boardman in the June, 1917, issued of the AMERICAN JOURNAL OF ROENTGENOLOGY, dealing with cases of coal dust inhalation and reviewing the roentgenologic literature on the subject. Both of these were published while we have not, therefore, felt that our work conflicts with that of the other investigators. It has been proven by all that the roentgenogram, supplemented by a careful roentgenoscopic study, is by far the most accurate means of studying the effects of dust upon the lungs. The pathology of the disease has been well established by autopsy, and roentgen obser-

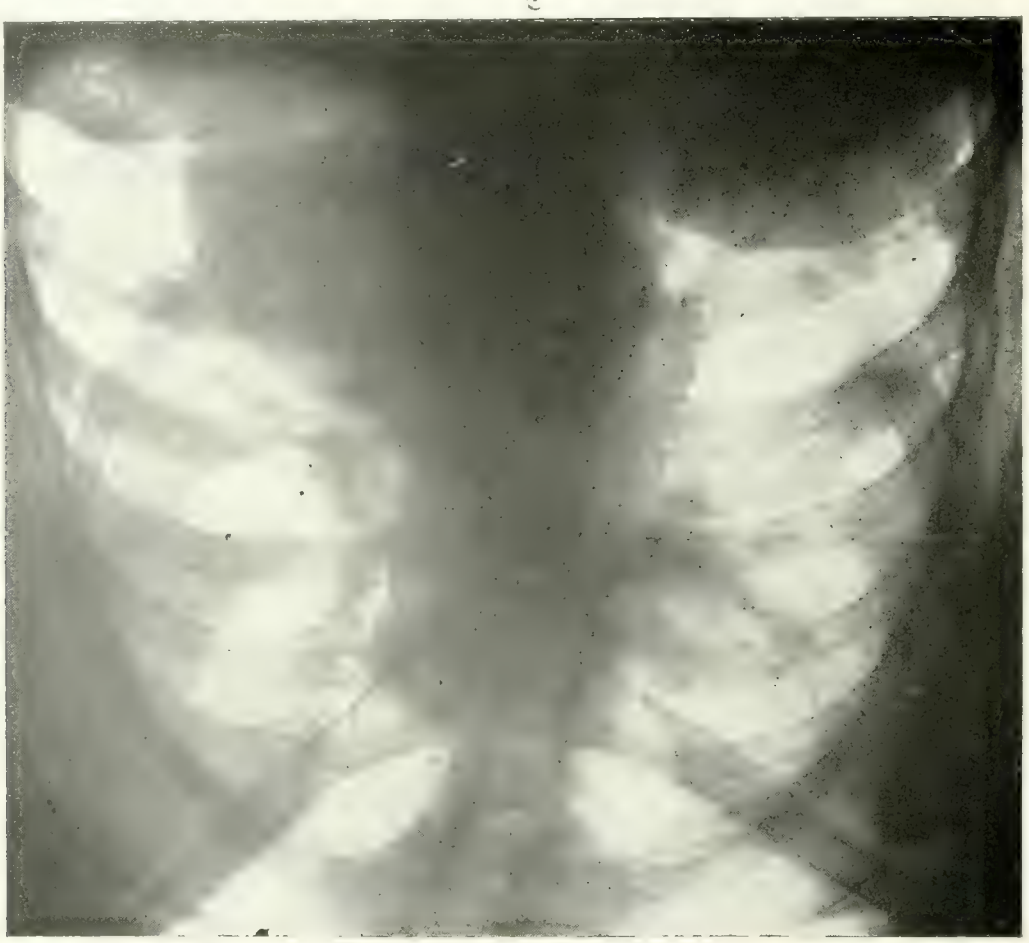

FIG. 4. PNEUMOCONIOSIS IN COAL MINER WHO WORKED THIRTY-EIGHT YEARS OUTSIDE THE MINES.

Roentgenoscopic examination; No interference with diaphragm excursion. Stereoroentgenograms: Increased hilus shadows, linear markings obscured, diffuse pneumoconiosis, with discrete spots, distributed from bases to apices, somewhat more marked on the right side where fibrosis is beginning. Note also the fibrosis in the subapical region. There were no unusual chest symptomes. This is a transitional case between the second and third stages.

were in the midst of our investigations, and it is interesting to note that the conclusions drawn by all of us, working independently, from the roentgenologic standpoint, have in the main been very much the same, differing only in minor details. Each of the above contributions has dealt with pneumoconiosis of a single origin, whereas we are endeavoring to study the condition as it arises from as many occupations as possible, and we vations serve to accurately portray th exact conditions *in vivo*.

Practically all roentgenologists ha had more or less opportunity to exami cases of pneumoconiosis, but most these have been isolated examples of advanced stage of the condition. order to comprehend the various phas and to suspect and recognize the whenever seen and, most important, differentiate the appearances of pne

moconiosis from those of other conditions, particularly tuberculosis, one must make a systematic study of the roentgen pathology through all the stages and from the standpoint of every source of invasion. When one realizes the very numerous occupations that provide sufficient dust to induce changes in the lungs, and the fact that dwellers in some large cities are subjected to sufficient dust to produce perceptible shadows in the lung structure, it seems quite probable that errors in diagnosis must be frequent unless the possibility of pneumoconiosis be constantly borne in mind.

Fig. 5. Pneumoconiosis in Coal Miner Who Worked Thirty Years inside the Mines.

Roentgenoscopic examination: Diaphragm almost fixed. Stereoroentgenograms: Extreme fibrosis of the third stage, with greatest density in subapical regions, where the density simulates consolidation. Emphysema at bases. Bronchiectasis left side. Intense dyspnoea. Repeated sputum examinations negative.

Three stages are to be recognized in the progress of the condition. In order to explain the condition itself and the changes which take place brief reference must be made to the pathology, which is very simple. The first marked effect of excessive dust inhalation is irritation of the air passages which amounts to a chronic bronchitis. This in itself is responsible for more or less fibrous change which becomes legible in the roentgenogram as a thickening of the trunk shadows. This is no doubt also due to a certain amount of dust deposition in the cells and neighboring lymph structures. The thickened trunks and the lymphatic structures with increased density tend to increase the size and density of the hilus shadows. Added pigmentation of cells and increased depositions of dust particles in lymphatic structures further out along the branching systems of the air passages gradually produce small areas of such density as to be visible and give to the lungs the characteristic mottled appearance so common in advanced cases of pneumoconiosis. Our experience has shown that this density is more or less closely related to that of the dust inhaled, being least in organic dust and greatest among metal grinders. Natur-

ally the fibrous change that starts early from irritation increases, and there is later a decided fibrosis following up the deposition of dust. This seems finally to involve a large part of the lung structure and is no doubt responsible for the dyspnœa by rendering the lung inelastic, which is readily determined by the lack of expansion noted by the fluoroscope, and particularly in the diaphragm. Bronchiectatic cavities are quite common in the late stages, and a similar process is manifest in the ultimate divisions of the passages as emphysema. The division of the process into three stages seems to be a foregone conclusion among those who have made a study of the subject. Before any access to literature could possibly modify our views, we had made practically the same classification which has been presented by the authors already referred to.

The first stage, roentgenologically speaking, is characterized by an increase in the hilus shadows and thickening of the usually prominent trunk shadows, and an undue prominence of the finer linear markings. This is due to the causes just mentioned. It is the rule that the increase in thickness of bronchial trunk shadows is fairly uniform, which is the main dependence in distinguishing the case from one of peribronchial tuberculosis, but threre are exceptions, and it is these which make the roentgenologic diagnosis difficult or uncertain. Boardman aptly calls attention to the fact that roentgenologists have no doubt been mistaking early evidences of pneumoconiosis for tuberculosis. If the distrib

Fig. 6. Pneumoconiosis in Potter, Forty-Five Years' Occupation.

Roentgenoscopic examination: Almost complete fixation of diaphragm (intense dyspnoea). Stereoroentgenograms: Hilus shadows increased; linear markings obscured; emphysema bases; dense mottling becomnig conglomerate, especially toward apices; extreme diffuse fibrosis, with bands to diaphragm, and heart and vessels drawn to the left; bronchiectatic cavities both subapical regions. Repeated sputum examinations negative.

tion of the thickening is regular, as it requently is, and the trunks to one apic- region only are involved, the two con- itions are quite difficult to distinguish y the inexperienced observer, and often most impossible to differentiate by ven the most experienced. A still more ifficult problem is the detection of a eribronchial tuberculosis in the pre- them, however, in the first or even the second stages. When the excursion has been equally shallow on both sides in the first stage, we have frequently been unable to decide that this was not due to habit or to inability of many individuals of the labouring class to "show off" their diaphragms to best advantage. The position of the excursion during ordin-

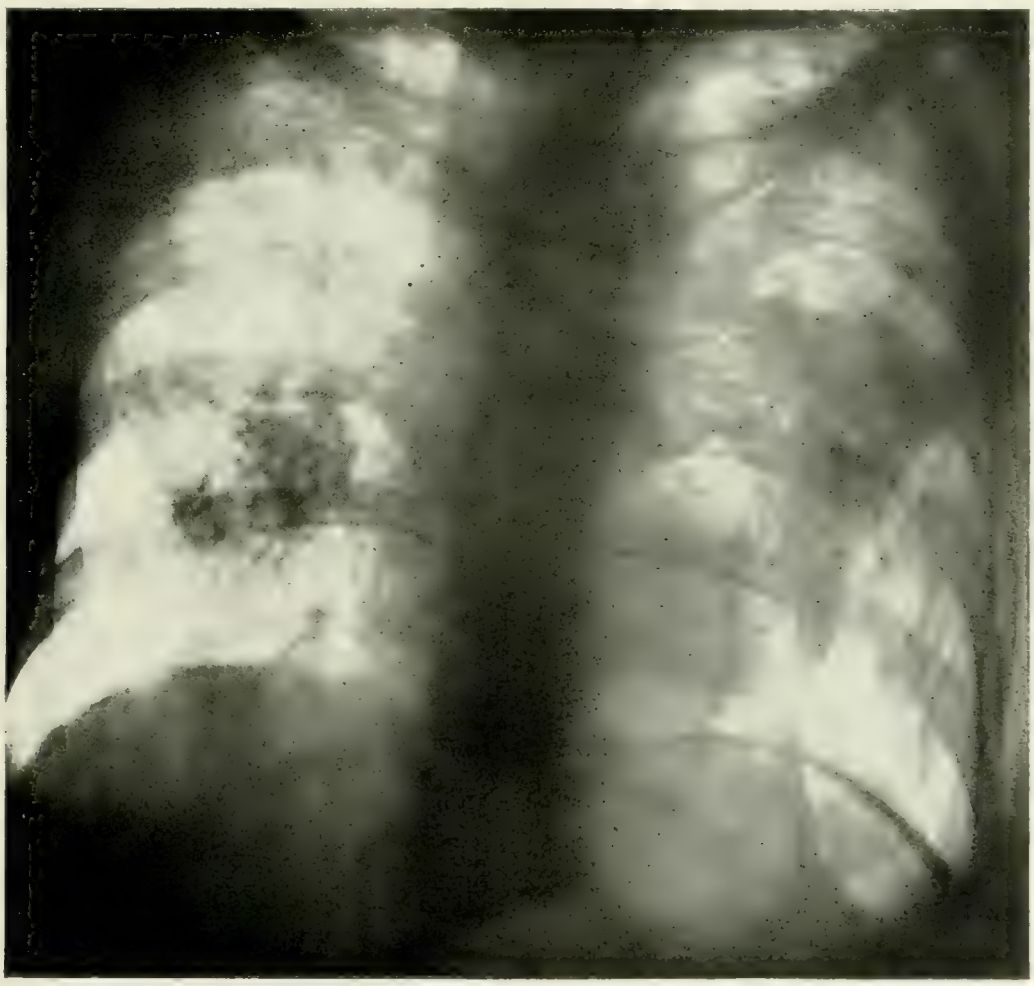

Fig. 7. Pneumoconiosis in Potter, Forty-Two Years' Occupation.

Roentgenoscopic examination: Right diaphragm fixed at mid-point. Heart and vessels pulled to right. Emphysema at bases. Stereoroentgenograms: Hilus shadows and linear markings uncertain; dense mottling still visible but becoming conglomerate; extreme fibrosis in both apical and subapical regions. Repeated sputum examinations negative.

ence of evidences of the first stage of neumoconiosis. In several instances e have recorded our plate readings as uspicious but we have not yet checked nese up with the clinical findings. Ab- ormalities in the diaphragm excursion re to be included in all the stages of ne condition. We have certainly noted nem in many instances in the first stage, ontrary to the experience of Lanza and hilds. There is no general rule about ary respiration between the limits of extreme inspiration and expiration is very variable. The most common finding was a restriction at the inner portion of the right diaphragm during full inspiration and either a decided flattening or a concavity of the outer aspect. It seemed as though the inner portion were halted in its descent by the process responsible for the thickened trunk shadows. It was our impression that the descending trunk

shadows were usually more thickened on the right side than the left, but the interference offered by the cardiac shadow prevented a satisfactory proof of this supposition.

The second stage is characterized by a more or less uniformly arranged mottling throughout the lung structure due to depositions of dust in the lymph structures, cells, and fibrous tissue inter-

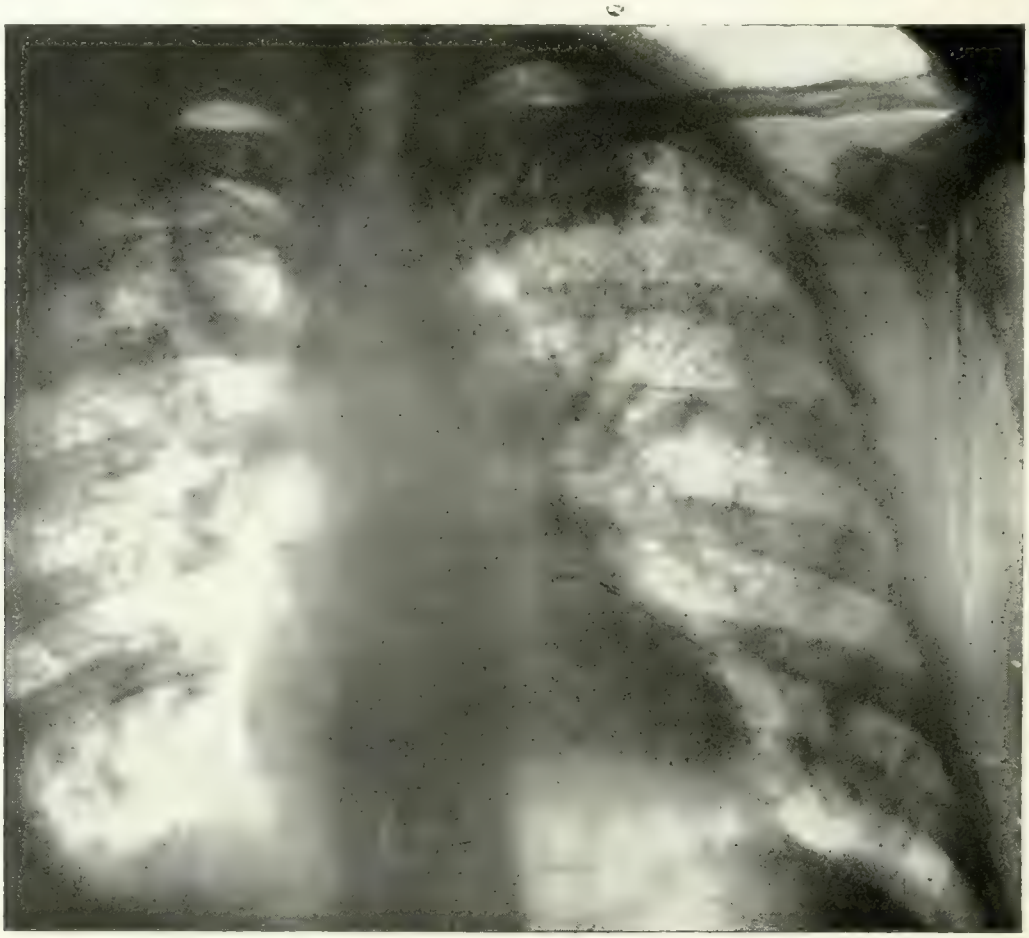

Fig. 8. Pneumoconiosis in Potter, Twenty-Nine Years' Occupation. Dense mottling throughout both lungs. The appearance at the left apex suggests an associated tuberculous process.

spaces, with the addition of a certain amount of localized fibrosis. This stage comprises what has usually been regarded as the typical case of pneumoconiosis. Its onset seems to depend largely upon the quality of the dust inhaled. It occurs comparatively early in coal miners, cement workers and certain metal grinders, somewhat later in potters and asbestos workers, and quite late in those inhaling organic dust. The volume of dust will, of course, enter into the statistics of this aspect of our work, and while this has been measured by Dr. Miller, comparisons have not yet been made. In metal grinders it was quite noticeable that mottling was observed before the usual first stage appearances were well advanced. Cement, asbestos and carpet mills were the dustiest buildings examined by Dr. Miller, but no computations were made in coal miners. On the whole, it has been our experience that certainly quality and probably weight or density are more important factors in pneumoconiosis than quantity, contrary to the statement of Boardman. The distribution of the mottling is interesting. Invariably we have found it first appearing in the right lung, on a level with the hilus shadow, which is quite contrary to the statements of Lanza and Childs. It certainly becomes quite perceptible on the right side before it appears on the left, and for some time after it does begin on the left side, it is noticeably more marked on the right. Later on it is impossible to demonstrate any dif-

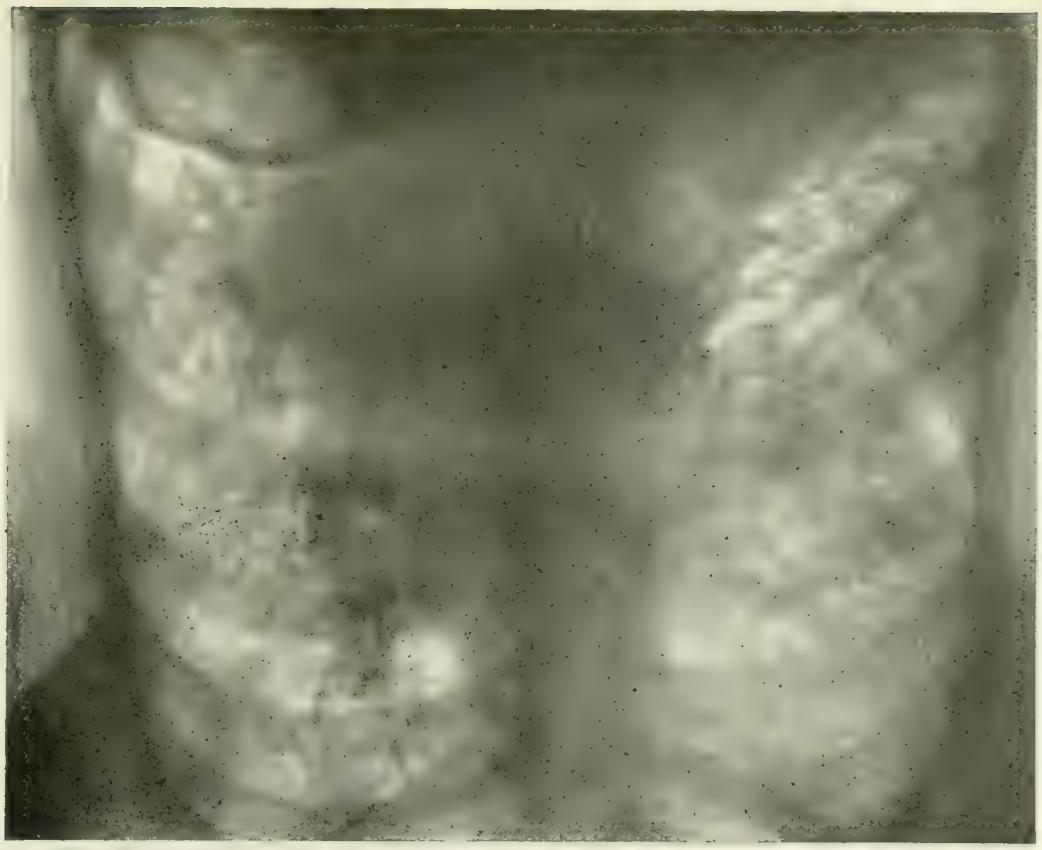

Fig. 9. Chest of a Male Aged Twenty-Nine, Who, When a Child, Inhaled a Vegetable Burr: Resulting Fibrosis.

The appearance is that of an extreme fibrosis which prolonged clinical study has proved not to be tubercular in origin. In the right base are numerous bronchiectatic cavities which, under the fluoroscope, could be seen opening on inspiration and collapsing on expiration. Compare this with fibrosis due to pneumoconiosis.

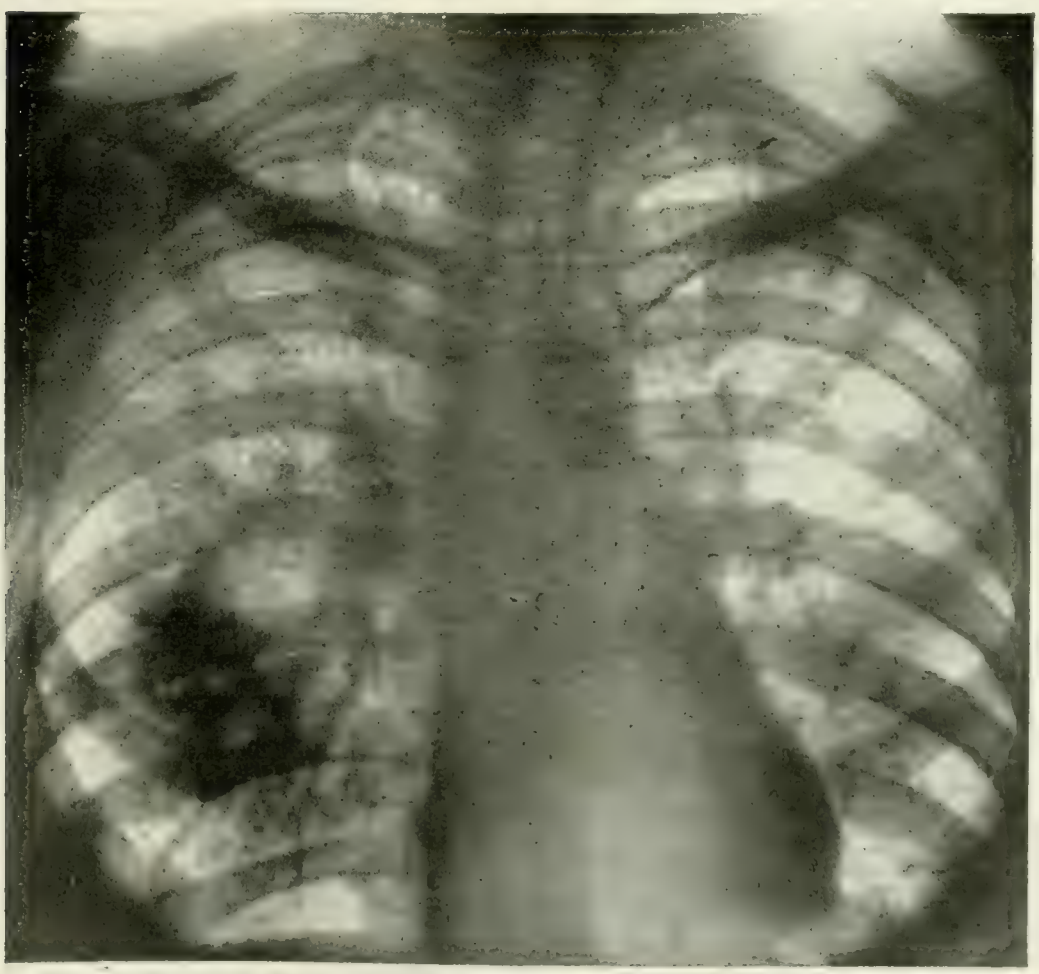

Fig. 10. Old Healed Pulmonary Tuberculosis Involving Right Lung, with Resulting Fibrosis.

Large bronchiectatic cavities previously found are now irregular in shape. The left lung is the seat of a more recent process now healed clinically. Compare with fibrosis due to pneumoconiosis.

ference on the two sides. The distribution is more or less symmetrical, but naturally not uniform, throughout the lung. From the starting point it gradually spreads to the bases and apices, but is never so marked at the extreme apices or bases as around the mid portion of the lung. The appearance of the mottling depends more or less upon the quality of the dust. In certain metal grinders the spots are very dense and sharply circumscribed and can be seen when very small. This is so to perhaps a less extent in coal miners, potters, and probably many other occupations. In cement and asbestos workers, among the inorganic dust occupations, the spots are noticeably softer and less sharply defined and the appearance is more like the early individual or conglomerate tubercle. In the organic dusts there is still further difference. Toward the end of the second stage the spots tend to enlarge and become conglomerate.

Errors in diagnosis are not so apt to occur in this stage. The appearance is so typical that no one is likely to mistake it for tuberculosis except possibly the miliary or bronchopneumonic types, and the history of the case is all that is necessary to correct any tendency to error. In a case examined without history, the distribution of the spots in the early stage and the comparatively slight amount of mottling in the apical regions later should put one on guard to ask questions. Here again, however, it may be exceedingly difficult to detect an early tuberculosis engrafted upon a well advanced case of pneumoconiosis in the second stage.

The third stage is the most interesting period in this condition from the roentgenologic standpoint. It is characterized by the appearance of diffuse fibrosis and all that the term implies. As an end result it does not differ greatly from the fibrosis that represents the terminal stage of chronic tuberculosis or some other less common causes. It is sometimes difficult to draw the line between the end of the second and the beginning of the third stage, and we are as yet uncertain as to the appearance at the period of transition. In some instances it would seem that the mottled appearance becomes increasingly conglomerate and passes over into the appearance of dense fibrosis, sometimes closely resembling consolidation. In other instances a general haze seems to spread over a certain portion of lung, resembling a thickened pleura in a flat plate but resolving itself into lung structure in stereoscopic plates. The greatest density is in the subapical regions, although this is not the region of most intense mottling in the second stage. We have imagined that the marked emphysema usually present at the bases must have some bearing upon this distribution. Dense fibrous bands can be seen extending in various directions, and frequently to the diaphragms, causing marked retractions. The heart and vessels are frequently dragged out of place. Bronchiectatic cavities are quite common. There is a very noticeable effect of inelastic lung structure upon respiration as studied by the fluroscope. The ribs move little enough, and the diaphragms sometimes not at all. Is it in the least surprising that these unfortunate individuals suffer intensely from dyspnœa? In this stage the mottling has become extremely coarse and sometimes is to be no longer recognized as such.

The differential diagnosis between the fibrosis resulting from tuberculosis and pneumoconiosis is frequently a most difficult problem, and, we have had to acknowledge, sometimes well-nigh impossible. It has been hard to believe that some individuals have not had tuberculosis; but repeated sputum examinations, sometimes over a number of years, have been negative. Still more difficult frequently is the detection of a tuberculosis engrafted upon this stage of pneumoconiosis. Suffice it to say that our studies have convinced us that errors in diagnosis have been made with considerable frequency.

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THE TREATMENT OF DIABETES COMPLICATING PULMONARY TUBERCULOSIS BY THE ALLEN FASTING METHOD[1]

H. R. M. LANDIS, ELMER H. FUNK and C. M. MONTGOMERY

Philadelphia

Although diabetes and tuberculosis have been known since the earliest times, the study of the association of the two diseases is of comparatively recent interest. The credit for the first report of a large number of diabetic cases, with special reference to tuberculosis of the lungs, belongs to Greisinger (1859), who records 250 cases. Windle, in 1883, reported the autopsies of 333 diabetic patients, with mention of the pulmonary conditions. Following Koch's discovery in 1882 tubercle bacilli were found in the sputum and lungs of diabetic patients (1883), and tuberculosis was produced in animals by inoculation with the sputum. Tuberculosis complicating diabetes has even been found in animals. Schindelka reported pulmonary tuberculosis in a diabetic dog, and Berenger-Ferand observed cerebral tuberculosis in a diabetic monkey.

A number of authors have been impressed with certain points of similarity between tuberculosis and diabetes. Thus Sauvage speaks of the interference with nutrition in the two diseases, the abundant elimination of waste products in the urine, both organic and mineral, and the diminished respiratory activity. Shively points to the progressive course in both diseases, to the emaciation, to the great fatality in early life, and the better resistance in later life, to the strong racial affinities, to their greater prevalence in cities than in the country, and to various other conditions common to both tuberculosis and diabetes. Purdy states that the "territories furnishing the highest mortality from diabetes in the United States coincide very closely with those furnishing the highest mortality from consumption. The very frequent termination of diabetes in consumption lends significance to this fact."

[1] Read before the Clinical Section of the Fourteenth Annual Meeting of the National Tuberculosis Association, Boston, Massachusetts, June 8, 1918.

THE FREQUENCY OF TUBERCULOSIS IN DIABETES

In a previous study by one of us (Montgomery) it was pointed out that tuberculosis did not occur more frequently in diabetics than in the general population at the same age periods. Out of 111 cases of diabetes collected in the hospitals of Philadelphia, 9 had active pulmonary tuberculosis and 1 other had adrenal tuberculosis. Out of 51 non-fatal cases of diabetes, none had active pulmonary tuberculosis. Out of 60 fatal cases of diabetes, 9 had active pulmonary tuberculosis and 1 other had adrenal tuberculosis. Out of 35 fatal but non-autopsied cases of diabetes, 3 had active pulmonary tuberculosis. Out of 25 post mortems, 6 showed active pulmonary tuberculosis and 1 tuberculosis of the adrenal gland without tuberculosis elsewhere. Out of 86 non-autopsied cases (35 fatal) 3 had active pulmonary tuberculosis and 17 more had signs recorded that were only slightly suggestive of tuberculosis. Out of 355 autopsies collected from the literature since 1882, including Montgomery's 25 cases, 138 (38.9 per cent) revealed pulmonary tuberculosis mostly in the acute form.

THE FREQUENCY OF DIABETES AND GLYCOSURIA IN TUBERCULOSIS

The occurrence, on the other hand, of diabetes and glycosuria in tuberculosis as a general proposition considered comparatively infrequent by various writers. Among 31,834 cases of tuberculosis, collected from 25 tuberculosis sanatoria and hospitals in various parts of the United States, there were 101 (about $\frac{1}{3}$ of 1 per cent) cases of glycosuria and 51 (about $\frac{1}{6}$ of 1 per cent) cases of diabetes. Some of the cases classed as glycosurics were undoubtedly diabetics, so that the percentage of diabetics may be assumed to be between $\frac{1}{3}$ and $\frac{1}{6}$ of 1 per cent of all these tuberculous cases. Autopsy statistics vary somewhat as in the following table:

	PULMONARY TUBERCULOSIS	DIABETES MELLITUS
Reports of the Surgeon-General, Public Health and Marine Service, 1895 to 1905	373	0
Henry Phipps Institute until end of 1910	479	1
Jefferson Hospital Tuberculosis Department	110	1
Adami and McCrae: Pulmonary Tuberculosis with Cavity Formation	85	4
	1,047	6

These figures show 6 cases of diabetes among 1047 post mortems. It is possible that Adami and McCrae's cases of diabetes were admitted as diabetics and not as consumptives, as their report is based on general hospital cases and not on cases which are all admitted primarily for their tuberculosis.

CLINICAL ASPECTS OF TUBERCULOSIS IN DIABETES

It is not our purpose to discuss the clinical aspects where these two diseases are associated. There are, however, several points of interest. *Hemoptysis* is stated as relatively rare. Von Noorden noted its occurrence in about 12 per cent of the cases of tuberculosis complicating diabetes. Sandwith did not observe it in any of the cases coming under his notice in Egypt, and Williamson invariably failed to meet with it even in cases observed up until the time of death. Shively, on the other hand, found hemoptysis to be frequent and considerable in amount in 4 out of 6 cases. In the 12 cases herewith reported it occurred in every instance except one. *Tubercle bacilli* in the sputum appear in large numbers, according to Immerman and Rutimeyer, but the majority of writers consider that they occur rarely or not at all (von Noorden). Von Noorden himself failed to find them in 4 open cases with copious sputum, and in a fifth (far advanced) case only after repeated search were a few tubercle bacilli found. In the lungs from this patient the cheesy nodules and their walls revealed masses of tubercle bacilli. Shively in 6 cases found tubercle bacilli present in 3 and absent in 3. In the 12 cases which we have studied the sputum contained tubercle bacilli in 10 instances. In a personal communication McCrae tells us that of 4 cases among his private records, tubercle bacilli were present in all.

TREATMENT OF DIABETES MELLITUS COMPLICATED BY TUBERCULOSIS

The combination of diabetes and tuberculosis in the past was sufficient to render an almost hopeless prognosis. The problem presenting itself was that of one disease requiring dietetic restrictions and the other requiring an abundant diet. The treatment was unsatisfactory because in most instances the tuberculosis was considered paramount and the diabetes less important. We now know that it is vitally important to control the diabetes first of all, at the same time instituting other measures for the tuberculosis, such as rest, etc., as are com-

patible with the diabetic treatment. A renewed interest in the treatment of the two diseases was brought about by Allen's work on diabetes. Allen showed that diabetes was a "specific deficiency of the power of assimilating food" and that there was a lowered functional capacity, not only for assimilating carbohydrates, but also for proteins and fats, and that the object of treatment was the supplying of a diet below the assimilation limit in order that an increase in the tolerance for the various foods might be acquired. In tuberculosis, where so much is dependent upon the ability to take and assimilate a diet of maximum value, the correction of any "specific deficiency in the power of assimilating food" becomes of first importance. We believe that it is absolutely necessary to accomplish this before it is possible to treat the tuberculosis effectively.

It may require considerable courage to make the tuberculosis patient fast for two, three, four or five days and then place him on a restricted diet for weeks afterward. We are encouraged, however, in practising this treatment to see after a while how a previously reduced tolerance for sugars and fats is improved and how the patient, after a preliminary loss of weight, will start to gain on a diet which under previous conditions would have resulted in a still further loss.

Twelve cases of pulmonary tuberculosis associated with diabetes were carefully studied; 10 were males and 2 females. Their ages were 28, 32, 37, 43, 48, 48, 49, 50, 52, 53 and 69 years. One case was incipient, 5 were moderately advanced, and 6 were far advanced. One revealed questionable activity, 3 slight activity, 2 moderate activity, and 6 considerable or marked activity. The prognosis in 6 cases was doubtful and in 6 unfavorable. In 7 of the 12 cases fasting was practiced at the start, in 2 for 5 successive days, in 4 for 3 successive days, and in 1 2 for days before the urine became sugar free. In all of the cases except one, fast days were ordered at various times during the course of the treatment.

In 5 of the 12 cases the urine could be rendered sugar free on a standard carbohydrate-free diet plus various additions to this diet, including a moderate amount of carbohydrates. These were evidently patients with some carbohydrate tolerance. One patient, however, could be kept sugar free only by ultimately resorting to fasting. Nine of the patients exhibited amelioration in symptoms and the improvement was noted as follows:

1. Weight (+10¼ pounds), strength, cough, expectoration, fever.
2. Weight (+11¼ pounds), strength, cough, expectoration, fever.
3. Weight (+3¾ pounds), strength, cough, expectoration, fever.
4. Weight (+ 1 pound), strength, cough, expectoration, fever.
5. "Felt better."
6. Weight (+ 8 pounds), strength, cough, expectoration, fever.
7. Weight (+ 5 pounds), strength, cough, expectoration, fever.
8. Weight (+ 15 pounds), strength, cough, expectoration, fever.
9. Weight (+ 10 pounds), strength, cough, expectoration, fever.

PHYSICAL SIGNS

In 5 of the 9 cases just mentioned physical signs did not change while the patients were under observation. In one, rales which were not noted on admission became audible at one base. In 3 the number of rales at the apices were considerably reduced. Three of the 12 patients showed progressive tuberculosis, 2 finally dying. There is no evidence of any causative relation between the dietary restriction and the unfavorable course of these 3 cases. As these results stand we can say that it is possible for patients with tuberculosis and diabetes to partake of a considerably restricted diet over a period of some weeks and still show an increase in weight and strength, a fall in temperature, and a lessening of respiratory symptoms. Whether these results in our cases would have been still more favorable on a more generous diet, or whether the progressive cases owe their failing health in any measure to the dietary limitations, cannot be stated. Nor has it been determined whether the reduction in the amount of sugar in these cases has had any effect on the pulmonary process. Other conditions being equal, we feel that prompt treatment of the diabetes according to the method of Allen offers the tuberculosis patient the best chance in the ultimate effort to control the tuberculosis. This is well illustrated by reference to the following case histories:

A. M., male, age forty-one, admitted to the White Haven Sanatorium December 5, 1916.

Family History. Mother died at sixty-nine years of age of diabetic gangrene.

Personal History. Fifteen years ago had hemorrhages from the lungs, for which he was sent to Colorado, where after a short time he gained in weight and became free from symptoms. Since that time he has had numerous attacks of blood spitting, and some years ago was told by a doctor that he

had sugar in the urine. Within the past two months he has developed a frequent productive cough, pronounced weakness, chilliness and fever, and loss of weight from 190 to 160 pounds. Upon admission he was quite sick, chilly and spitting blood.

Physical examination. There were signs referable to the upper right lung. There were abundant crackling râles at the right apex and a few at the left apex. The sputum showed tubercle bacilli. The urine on four successive days varied in its specific gravity from 1035 to 1040, and showed sugar in amounts from 3.4 to 4.6 per cent and a faint reaction for diacetic acid.

Treatment. The patient was placed at rest in bed in the open and on the regular house diet to determine the degree of glycosuria. He was then fasted for two days before he became sugar free, when he was given 200 gm. of 5 per cent greens. Subsequently the diet was increased, as per the attached chart. During the administration of the treatment hemorrhages occurred and continued almost daily in varying amounts up to 9 ounces, until after a period of approximately two weeks it was deemed imperative to induce pneumothorax when a sudden cessation followed. The subsequent course of the tuberculosis and diabetes was favorable, as is well shown in the attached weight, temperature and other charts. Shortly before discharge, which was demanded because he felt so well, the patient indulged in several dietetic indiscretions with a consequent derangement again of the sugar tolerance. We feel confident that in this particular case if the patient had remained under treatment sufficiently long and with acquiescence to the dietetic restrictions, he could subsequently have reached a point where with a fairly liberal diet he would have made further gains in weight, remained sugar free, and continued to arrest more and more tuberculous lesion. It was most interesting to observe the results of treatment in this patient which was instituted in the presence of recurring pulmonary hemorrhages that ultimately required therapeutic pneumothorax.

S. H., female, age forty-three came under observation in our private practice on November 10, 1917.

Family History. Mother died of tuberculosis.

Personal History. Patient has coughed for many years and spat blood several years ago. Recently, that is during the last three or four months, she has lost weight in spite of an unusually good appetite and digestion. Her average weight is 145 pounds, present weight 125 pounds. Her cough has become aggravated and associated with expectoration. Coincident with the loss of weight there has been pronounced weakness with an afternoon fever of 99.4 to 100°F.

Physical Examination revealed an old chronic tuberculosis with infiltration of the upper portions of both lungs. The sputum contained tubercle bacilli. The urine showed a marked reaction for sugar when 5 to 8 drops were added to 5 cc. of Fehling's solution.

Treatment. The patient was placed at rest in bed and fasted for three days, when the urine became sugar free. The patient was then placed on 200 grams 5 per cent greens and the diet gradually increased until a tolerance of 160 grams carbohydrate was reached, beyond which it was not possible to go without developing glycosuria. At the end of three weeks the temperature became more normal, and the cough lessened, but the weight dropped 8 pounds to 117 pounds. Subsequently, however, there was a gradual improvement, until in January the patient weighed 130 pounds, and on April 10th, 132 pounds. Coincident with the general improvement of the patient there was a marked improvement in the local symptoms and signs, and when last seen the patient was on three hours' exercise.

M. Y., female, age forty-two, admitted to the White Haven Sanatorium October 23, 1917.

Family history. Father died at sixty-five years of age of pleurisy. Mother died at seventy-five years of age of pneumonia.

Present illness dates from a cold in June, 1917, since which time she has had a constant cough and expectoration with progressive loss of weight. One hemoptysis occurred in September, 1917. During the last three months she has had considerable dyspnea at times, and without exertion. The appetite is poor; the bowels are constipated. She weighed 200 pounds in June, 1917, and upon admission in October, 1917, 157 pounds, a loss of 43 pounds in four months. During the past month at home she has felt quite sick and unable to do ordinary housework.

Physical examination reveals a pallid adult female who appears quite sick. The lung examination reveals bilateral tuberculous disease with extensive involvement of the left side where the signs are those of consolidation of the entire upper lobe. The right lung shows signs of infiltration at the apex. The heart is normal. The sputum shows many tubercle bacilli. The urine contains 4.3 per cent sugar and a trace of acetone and diacetic acid.

Treatment. After three days of fasting the urine became sugar free, whereupon the patient was started on a diet containing 200 grams of 5 per cent greens. The diet was subsequently increased in the same manner and to the same level approximately, as in the case of A. M., whose chart is appended to this article.

In spite of the fact that she was kept sugar free by this diet and an occasional fast day, she progressively lost in weight to 118 pounds. The tuberculosis seemed stationary, as far as physical signs were concerned, and the constant dropping off in weight, with the marked weakness, lead us to believe that we ought to increase her diet. This we did, with the result that she promptly gained about 15 pounds in a period of two months so that she now weighs in the neighborhood of 130 pounds, the urine continuing sugar free. She is now (December 30, 1918) considerably stronger, is afebrile and is

allowed all day cure. In this particular case we feel that we kept the patient on a reduced diet too long. Every effort ought to be made to ultimately bring the diet up to a maximum for these patients, or to approximate the maximum diet that is given to tuberculous patients, provided of course, that the urine continues to remain sugar free.

The following case illustrates how in the presence of severe diabetes and advanced tuberculosis a temporary improvement may be secured.

C. B., male, age fifty. Ten months ago, following the grippe the patient developed cough, expectoration, and loss of weight. Six months ago he had a frank hemoptysis. His average weight of 165 pounds has become reduced during the past four months to 137 pounds.

Physical examination reveals advanced bilateral tuberculosis of the lungs with a large cavity in the left apex. The sputum contained many tubercle bacilli. The urine contained 5 per cent sugar.

Treatment. The patient was placed absolutely at rest in bed and for two days the ordinary diet was cut to less than half. Sugar continued to be present in the urine. The patient was then fasted for three days, when the urine became sugar free. He was then given 250 grams 5 per cent greens and sugar reappeared in the urine. He was then fasted for two more days and the urine became sugar free, whereupon he was started again on 250 grams of 5 per cent greens, and by the gradual addition of 5 grams carbohydrate every other day, his tolerance was gradually raised to 75 grams. The symptoms referable to his tuberculosis were for a time definitely improved, although subsequently, as a result of the extensive lesion, the disease again became quite active.

In a disease like tuberculosis which affects its victims in such a variety of ways and with such uncertain results, it would be unsafe to draw conclusions as to the action of a special mode of treatment unless the number of patients was sufficiently large. In our 12 cases, however, we have felt that we have learned this lesson: first that in order to make any progress the diabetes must be controlled first of all, secondly that the fasting method of Allen offers the most prompt method of controlling the diabetes, and thirdly, that in the application of this method the following plan formulated by Allen is practical in tuberculous patients:

1. A preliminary fast until the urine is free from sugar.
2. Following the fast, the gradual addition of carbohydrate, at first in the form of green vegetables.
3. Coincident with the addition of carbohydrate, or in place of it,

if the carbohydrate tolerance is very low, the addition of protein to the diet in small but gradually increasing amounts until glycosuria occurs, or a sufficient amount of protein is taken to cover the basal requirement.

4. The addition of fats in small amounts during the time of addition of carbohydrates and protein. Subsequently, a sufficient amount of fat is added to make up the fuel requirements of the body, provided this amount can be tolerated without the appearance of glycosuria or acidosis.

5. Frequent urine examinations are made, either by the physician or by the patient himself, and the appearance of sugar is taken as an indication for a fast of sufficient length to cause a cessation of the glycosuria. Feeding is subsequently begun with not more than one-half of the carbohydrate contained in the diet at the time of the appearance of glycosuria. The subsequent carbohydrate increase is made very gradually.

6. At intervals, the patient is fasted for a day or else takes a greatly restricted diet.

Rest in bed, rather than exercise, as is advised in ordinary diabetics is necessary because of the tuberculosis; and special care is necessary in order not to increase the fats too rapidly in the desire to bring up the caloric value of the diet, for fear of producing acidosis, as in several of our cases. The treatment is applicable in the presence of recurring hemoptysis, and in every case of tuberculosis of the lungs unless the patient is obviously hopelessly ill with the pulmonary lesion, in which case, the institution of the antidiabetic treatment would add only further discomfort.

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THE MANAGEMENT OF FEVER IN PULMONARY TUBERCULOSIS.

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Fever constitutes one of the most, if not the most, important symptoms of pulmonary tuberculosis. Not only will a study of the temperature chart give a fairly accurate insight as to the type of disease, but in addition attention to the temperature variations is of the utmost importance as a guide to treatment.

The use of the thermometer in doubtful cases has been repeatedly urged as a diagnostic measure. The presence of an afternoon rise in the temperature if only to 99° or 99.1° may be the determining point in a case which has indefinite symptoms and slight or even an absence of physical signs. It seems hardly necessary to call attention to the fact that temperature observations in these cases are of little value if taken in the morning. The afternoon rise almost invariably begins about noon and is apt to be present for some hours. If the temperature is taken at noon, 4 and 8 P.M., it will show some elevation if an active process is present.

Another precaution is necessary. It is not generally recognized that even the minute and half-minute thermometer will often fail to indicate a temperature of 99.1° or 99.2° if left in the mouth for half a minute or a minute. Some years ago I made a series of observations at the Phipps Institute on this point. We found that for slight degrees of fever it was necessary to leave the thermometer in the mouth at least seven to ten minutes, and when this was done the three-minute thermometer was quite as efficient as the others. For temperatures over 100° F., the registration is very rapid. We also noted that the mouth temperature should never be taken within ten minutes of anything hot being taken in the mouth, and at least half an hour should elapse if cold substances have been taken. As to the relative merits of mouth and rectal temperatures we found that the former, under proper precautions, were as reliable as the latter. In addition the taking of rectal temperatures is often inconvenient and many patients object to the method. For practical purposes the oral method is sufficiently reliable and, in my opinion, the preferable one.

It is almost universally accepted the world over that rest during the active period of the disease is imperative, and the one symptom beyond all others that requires rest is fever. Years of experience have shown that it is by rest and rest only that fever is eventually controlled. At one time some of the various coal-tar derivatives were occasionally recommended for the reduction of fever, but entirely aside from their injurious depressing effects, they should never be employed. While it is true that they have a marked influence on the heat center and will temporarily cause a reduction of the temperature, it is only a transient effect. The cause of the fever remains untouched, and so long as this cause, namely, the tuberculous process in the lungs, continues active fever is almost certain to occur. There are a few exceptions to this, but in the vast majority of cases the presence of fever is to be looked upon as one of the strongest possible pieces of evidence that the disease is active; just as certainly as smoke is an indication of fire.

Alcohol is another remedy which the older writers recommended as being of service when fever was unduly persistent. I have never seen that it exerted the slightest influence in this regard.

Sponging is a symptomatic remedy that is often serviceable if the temperature is unduly high and persistently so both morning and afternoon. It only gives temporary

relief, however, and need not be used in those cases in which the temperature is normal or subnormal in the morning. Although the afternoon temperature often becomes very high, it remains so for but a relatively short time, and it is only exceptionally that measures are necessary to reduce it.

It has been claimed that tuberculin will sometimes dissipate the fever. The majority of those who are favorable to this form of therapy warn against its use in febrile cases.

It has become a more or less fixed procedure among the present-day phthisiotherapeutists to institute the treatment in all cases by a period of absolute rest in bed, and this regardless of the severity of the symptoms and the extent of the pulmonary lesions. Experience has shown that this rule is a safe one. It is only by experience that we come to learn that it is impossible, as the result of a single observation, to foretell the probable outcome in a given case or to form any idea of how long it will be necessary for the patient to continue treatment. In the case of a patient whose symptoms are not severe and the examination of whose lungs shows but slight pulmonary involvement, the temptation is often strong to assure him that two or three months will arrest the process. It is only after having the unfortunate experience of seeing such patients steadily and progressively go from bad to worse that we become wary of being too optimistic. It is much better to withhold one's judgment until the patient has been under observation *at rest* for at least one month. By this time one should be able to form some opinion as to the probable outcome. One of the strongest determining points is the presence or absence of fever. If the patient has no fever or whatever fever may have been present quickly subsides, one is usually justified in assuming that the disease is not very active. On the other hand, if fever is present and shows no inclination to subside when the patient is at rest, an active type of the disease is probably present.

In the event of the patient being febrile, how long is the rest in bed to be continued? Generally speaking, it should be an absolute rule to maintain the rest in bed until the temperature is normal and has remained so for a variable period. The continued rest after the febrile stage is reached will depend largely on the length of time it has taken to get rid of the fever. Thus if the temperature becomes normal in two or three weeks the patient should be continued at rest for a week or ten days longer before allowing him to sit up. On the other hand, if the fever has required three or four months' rest in bed to reduce it, the rest must be continued for a considerably longer time when the afebrile period is reached.

Upon being told that they will have to undergo a period of absolute rest in bed, patients usually want to know how long this will have to be. No time limit should be fixed. If a definite time is stated one is certain to regret it. It not uncommonly happens that a patient will show, in the beginning, a temperature of 102° F. or higher. One usually feels with such a temperature that it will take weeks and perhaps months before it will fall to normal, and yet every now and then such a case will have a normal temperature in two or three weeks.

On the other hand, the initial temperature observations may show a range from 99° to 99.3° F. and give every promise of subsiding quickly. Very often such a temperature curve is persistent and may take weeks and weeks before it becomes normal. Although no fixed rule can be given, the following table compiled by Burton-Fanning gives some idea of the length of time the various initial temperatures may take to become normal:

Average maximum temperature for first week of treatment.	No. of cases.	Percentage in which temperature became normal.	Average number of weeks required to reduce fever.
Between 99.0° and 99.5° F....	37	87.5	3.6
Between 99.5° and 100.0° F...	18	54.4	5.7
Between 100.0° and 100.5° F..	11	46.6	4.8
Between 100.5° and 101.0° F..	9	34.2	6.5
Between 101.0° and 101.5° F..	6	37.5	17.5

From a study of 716 patients under sanatorium treatment, Burton-Fanning found that 50 per cent lost their fever in an average of one month.

I would, however, again emphasize the fact that entire reliance cannot be placed on the degree of temperature when the patient is first placed under observation. Relatively high temperatures may subside quickly, and those which show but a slight degree of fever may persist for an indefinite period.

Having reached the normal level, what means have we of determining that this is probably permanent? Very often a patient will have had a normal temperature for weeks even after being up and about, although not on graduated exercise. During this period he may have a bilious attack or a mild attack of coryza. Such episodes are usually so trivial that in the normal, healthy individual they produce no elevation of temperature. In the tuberculous individual, however, they may cause a sharp elevation of temperature. If they do it is safe to assume that the tuberculous process is not arrested; it is only quiescent, and the most trivial thing will cause the appearance of fever, although usually transient in character. Under these circumstances one is safe in assuming that the temperature is still unstable, and unless one is cautious a return of the fever may be brought about.

How long should modified rest be continued after the temperature has become normal? If the patient has been very ill and the bed period has been a long one, he should be permitted to sit up for half an hour a day and increase this daily, providing no ill effects are produced. If, however, the infection is a mild one, and the bed period has not been over a month or six weeks, he can usually be allowed to get up and dress and take his cure in a steamer chair. This, of course, entails a certain amount of moving about. After a month of this modified rest, graduated exercise may be started. This is usually in the form of walking. The patient is started with a ten or fifteen minute walk, and this is increased two or three minutes daily up to one, two, or three hours. The increase is allowed to go on provided it does not aggravate the symptoms which are still slightly evident, as, for instance, cough or dyspnea, or there is no elevation of the temperature. If after the exercise, which should be taken in the morning, there is a return of the afternoon fever, no matter how slight, the modified rest must be returned to, and if this fails to restore the temperature to normal, rest in bed must again be resorted to. There is no use temporizing. The longer one defers taking this step the longer it is eventually going to take to reduce the temperature.

Although there is a unanimity of opinion among those of experience in regard to the absolute necessity of rest, especially at the onset, there is a sharp divergence of opinion as to the length of time the rest should be persisted in. There are some who are ultra-conservative and who continue the rest in bed for long periods of time irrespective of whether symptoms continue or not. While I believe that errors are most often made by restricting the rest period, I am equally sure that not a few patients are permanently injured by prolonging the rest period indefinitely. Long after they have become afebrile the rest is persisted in, with the result that the patient becomes unduly heavy and flabby, and more especially becomes skeptical as to his ability ever to do anything but lie about and avoid even the most trivial exertion. The inevitable sequence is an obstinate neurasthenic state that makes the patient a burden to himself and every one about him. This is not desirable, and it is furthermore questionable whether we accomplish very much by changing one condition into another. Our object, of course, is to first arrest the tuberculous process and, as soon as is compatible with the extent of the pulmonary lesions and the original severity of the symptoms, to restore the individual to something approaching his original condition. This can be done only by feeling our way with exercise, and in

my opinion the sooner this is undertaken the better. The longer one has to continue the period of absolute rest the longer it will take to inure the patient to exertion; and an added danger is, of course, the mental effect of being constantly cautioned against exertion. Therefore, between the two extremes of (1) indefinite rest in bed and (2) a foolish disregard of danger-signals, such as fever, increase of cough, loss of weight, etc., there is a middle course. In other words, patients should not be treated routinely but should be considered individually. So long as fever continues, or the weight remains stationary or untoward symptoms unexpectedly develop from time to time, rest must, of course, be continued. But when these evidences disappear, I feel very strongly that the trying out of the patient's resistance should be instituted as early as possible. Providing this is not done rashly and due regard is paid to whether the symptoms are aggravated by the exercise, no great harm will result. The patient should be cautioned that it is entirely a matter of experiment and that no one can foretell, in a given case, as to whether the taking of exercise will prove beneficial or harmful. He can be assured, however, that if he follows instructions and does not exceed the prescribed amount, little or no damage will result.

The question of determining the fitness of a patient for a reasonable amount of exertion has a distinct economic importance. The man or woman financially able to protract the treatment indefinitely can be carried along more gradually than the man whose resources are limited and who in addition has the responsibility of a family to support. Even if the patient is cared for in a free institution the expenses of his family go on, and the sooner he is restored to a wage-earning capacity the better. I do not wish to be understood that such patients should be pushed unnecessarily, but I would again emphasize the fact that it is bad economics as well as being bad for the patient to protract the rest treatment too long.

Another application of rest in the treatment of fever is the use of artificial pneumothorax. This method is simply applying to the diseased lung the surgical principle of putting a diseased tuberculous joint at rest. The compression of the lung by nitrogen gas or sterile air is analogous to the use of a splint. This method, which was heralded a few years ago as a cure-all, has lost some of its popularity as an agent which is generally applicable. It has, however, a very distinct place in the therapy of pulmonary tuberculosis, and one of its fields of usefulness is in the type of case which is obstinately resistant to the ordinary methods of treatment. In such cases, in spite of continued rest in bed and the usual hygienic and dietetic measures, the fever persists, the cough and expectoration continue unabated, the patient fails to gain or often gradually loses weight, and the physical signs are indicative of softening and breaking down of the lung tissue. Collapse of the affected lung, or if both are diseased the worst one, will at times bring about an extraordinary change for the better. During the past six months I have had two excellent examples of this at the White Haven Sanatorium. When first seen one of these patients seemed to offer every prospect of a rapid arrest of the disease; the other one was doubtful. From the onset both did badly. The temperature gradually assumed a higher range in the afternoon, there was loss in weight, and the cough gradually increased in severity. At the end of three months it became apparent that the ordinary methods offered little or no hope for an improvement. Artificial pneumothorax treatment was, therefore, advised. For four or five weeks each biweekly injection was followed by a temporary increase in the fever. At the end of this time, however, the temperature rapidly fell to normal, and coincidentally with this improvement in all other particulars soon became manifest. One of these patients has gained 22 pounds, is free from fever, and is taking two hours' exercise daily. The other bids fair to do the same thing,

although the general improvement, so far, has been less striking.

Under what circumstances can the rest treatment be modified if fever is present. There are two groups of cases to be considered. In the first place there is the chronic case of many years' standing. Usually the lung lesions are more or less extensive and cavity formation is commonly present. If such a case has never undergone treatment the method should be the same as that outlined above for the early case. If, however, the general condition is good and the patient has had one or more experiences with sanatorium treatment, slight elevations of the temperature (99°-99.3°) three or four times a week need not necessarily call for absolute or even modified rest. There are many such individuals, some of whom follow their daily employment, who have little or no trouble. How much latitude we will allow such a patient will depend a good deal on how long the disease has been present; whether the patient has been subjected to sanatorium treatment previously; and, lastly, his method of living. If the history indicates disease of long standing and the patient has learned his limitations, he can be trusted to be up and about and even work, although some slight degree of fever is more or less constantly present.

Finally we have to consider the management of the hopeless advanced case. A marked degree of afternoon fever is almost constantly present in these cases. Inasmuch as the outlook is hopeless we can afford to disregard not only the fever but other symptoms. Our object when this stage is reached is to make the patient as happy and as comfortable as possible. In most instances such patients had best be kept quiet and in bed, not because anything is to be expected in the way of improvement, but solely because they are usually more comfortable and suffer less annoyance from their symptoms. Some of them, however, chafe at the prolonged rest in bed; they insist they feel better when up and dressed, and in some instances claim that a little exercise relieves them. The outlook is almost invariably hopeless if a hectic type of temperature is present, the pulse-rate is 120 or higher, and a third of the body weight has been lost; if in addition one or more serious complications are present, a fatal ending is inevitable. Under these circumstances the patient may be allowed to sit up for a time each day and even get dressed if it makes him better satisfied, and at the same time does not aggravate the symptoms. Very often merely consenting to such an arrangement or one or two trials satisfy them that after all bed is the best place.

A word as to the diet. Fever is to be disregarded in so far as feeding the patient goes. It must be borne in mind that we are dealing with a wasting disease. Next to rest, our chief reliance in arresting the disease is by building the patient up and increasing his resistance. Loss of weight must be checked, and furthermore the loss already incurred must be restored. There is no need of following dietary fads. What is wanted is a liberal supply of wholesome, nourishing food. Three meals a day of an ordinary mixed diet, supplemented, if the loss in weight is marked, by six to eight glasses of milk, will give satisfactory results in the great majority of cases. It is necessary, of course, in some instances to have recourse to special kinds of food if the patient has a capricious appetite and an uncertain digestion.

THE PATHOLOGICAL AND CLINICAL MANIFESTATIONS FOLLOWING THE INHALATION OF DUST*

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"Failure to inquire respecting the occupation, and a want of knowledge of its working condition and customary ailments, places the doctor at a disadvantage toward his patient, and deprives the latter of the full benefit of treatment."—*Arlidge.*

INTRODUCTION

PNEUMOCONIOSIS occupies a curious position. The term is a familiar one and the nature of the disorder is described in all text-books dealing with diseases of the lungs. In spite of this, however, the term is rarely used by the clinician and only a little less frequently by the pathologist. Furthermore, one may search statistics dealing with morbidity and mortality rates and never find any mention of the condition. In those instances in which the deposition of dust in the respiratory system has actually given rise to pathological changes, the illness or the cause of death is ascribed to secondary changes, such as chronic bronchitis, asthma or tuberculosis. The etiological factor is thus concealed by the use of other terms. The reason that mild grades of pneumoconiosis are rarely mentioned as such is to be ascribed to the fact that a slight degree of pneumoconiosis is present in the lungs of all city dwellers who have reached adult life, the condition under such circumstances being regarded almost as normal. Furthermore, in the presence of the mild type or in the very early stages of the serious and progressive type there are no symptoms, nor is there anything abnormal to be found on physical examination. In the advanced stage the condition is usually referred to as fibrosis or cirrhosis of the lung. Now that the X-rays have come into general use, we have a ready method of determining the condition almost from its incipiency. In the future, pneumoconiosis, with or without fibrosis, will probably be used more generally as a distinctive term. An additional reason for bringing it more prominently to notice is the ever-increasing interest in diseases associated with certain occupations. There can be no doubt but that the whole subject of dust in its relation to disease is in need of more intensive study than has been given to it in the past. Collis (1) has stated that until recent years the tendency has been to consider, as a broad truth, that dust inhalation predisposes to diseases of the chest, of which pulmonary tuberculosis is the chief. "Closer investigation," he continues, "is proving that the subject is more complicated; that respiratory diseases caused by dust vary with the nature of the dust inhaled; that although a special type of pulmonary tuberculosis occurs upon the inhalation of certain dusts, it is not associated with the inhalation of all kinds of dust; and that other forms of chest disease, which, though not equally fatal, seriously impair the respiratory organs, are set up by inhaling special forms of dust."

Moreover, as has been pointed out by Pometta (2), it is to be borne in mind that there is scarcely any sickness from industrial causes that cannot develop, with about the same group of symptoms, from some entirely different cause.

The first systematic treatise on the effects of the inhalation of dust was con-

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tributed by Ramazzini (3) in 1700. From that time down to the latter part of the nineteenth century, the literature contains numerous references to the subject. Some call attention to the association of certain occupations with respiratory disorders, others have to do with the pigmented areas in the lungs and their possible association with dust. In 1838 Stratton (4) suggested the name anthracosis to designate the changes produced by the inhalation of coal dust. Since that time a number of terms have been used to indicate the particular variety of dust, namely, silicosis, siderosis (iron dust), etc. In addition a variety of popular names have been applied to the dust diseases, the terms used indicating the occupation, as for example, miners' asthma, black-spit, grinders' rot, potters' rot, potters' asthma. The preferable term is that suggested by Zenker—*pneumoconiosis* (πνευμων, lung; Κονις, dust).

Among the earliest observations may be mentioned those by Wafler (1729) and Le Blanc (1775) on the great mortality among the makers of French millstones; and Johnstone (5) on the mortality among the needle pointers of Worcestershire. Thomas Beddoes (6) quotes Linnæus to the effect that cutters of grinding stones all die phthisical before the thirtieth year. Beddoes also noted the frequency of this affection among stone cutters, needle grinders, brass workers and miners, but states that others, as japanners, millers, etc., are not subject to this disease. Beddoes was far ahead of his time in expressing the belief that the high death rate from phthisis among textile workers, tailors, glovers, etc., was to be attributed to confinement and inactivity rather than to dust.

In 1813, Pearson (7) first suggested that dust particles gained access to the lung tissue, and he attributed the dark pigmentation often met with in the lung to the actual deposit in it of particles of carbon or soot derived from the air. Similar observations by Christison (8) and Graham (9) confirmed this view. Virchow, however, denied that the pigmentation was due to carbon and attributed it to organic pigment from the blood. Among those who furnished the proof that the dust actually was deposited in the lung may be mentioned Traube (10), who discovered in the lung of a charcoal burner the angular particles of charcoal dust; Zenker (11), who showed by chemical tests the presence of iron dust and Knauff (12), who demonstrated by inhalation experiments particles of soot in the lungs of dogs. Finally in 1866 Virchow (13), himself, acknowledged that the proof was indubitable.

One of the most interesting and unique studies of occupations is that by Henry Mayhew entitled *London Labor and the London Poor; a Cyclopædia of the Conditions and Earnings of Those That Will Work, Those That Cannot Work, and Those That Will Not Work.* This book, published in 1851, is the first of which I have any knowledge to portray the life of the worker from every standpoint, namely, the character of his work, his hygienic habits, his amusements and his environment—both at work and at home.

Until the discovery of the tubercle bacillus by Koch, in 1882, no distinction was possible between extensive non-tuberculous and tuberculous fibrosis. The term fibroid phthisis was therefore very loosely used and, even at the present time, many cases of non-tuberculous fibrosis are classed as instances of tuberculosis. Tatham (14), in commenting on this aspect of the question, states that "it is certain that much of the so-called potters' phthisis ought properly to be termed cirrhosis of the lung. Deaths from this affection should never be included under the head of phthisis, which term is now restricted by universal consent to the tubercular malady of that name."

Among others who have written largely on the subject may be mentioned Thackrah (1832), G. Calvert Holland (1843), Arlidge and Oliver in England; Hirt (1871) in Germany; and Hoffman and Kober in this country.

ETIOLOGY

As the result of the rise and expansion of a wide variety of manufacturing interests during the nineteenth century, the attention of sanatarians became more and more directed toward the harmful effects of industrial processes. And of the various harmful agencies none has received more attention than dust. In England, because of the number and variety of her

manufacturing interests, the subject has received a great deal of attention. In this country but little thought has been bestowed on the subject until within the past decade. But if we have been backward in realizing the importance of the subject, there is no doubt that the period of apathy has passed. As Hoffman recently remarked, "no nation within recent years has equaled us, either in the quantity or the quality of the work done along the lines of industrial medicine." Much as is known regarding the effects of dust, there is still much to learn and, more important still, there is much to unlearn. At the present time there are too many statements made for which there is no adequate proof. In not a few instances statements regarding the harmfulness of certain dusts have become traditional and continue to be accepted by each succeeding writer on the subject. Many such statements are subject to revision. At the present time far too much of our knowledge regarding the evil effects of dust is based on mortality statistics. While we have no desire to discredit or belittle data of this sort, it is undoubtedly true that mortality returns give a very false idea in many instances, particularly in reference to the organic dusts. As a result of studies of this kind many industries have gained an evil reputation because of a high death rate from tuberculosis among the employees. It has been assumed by most writers that the dust is unquestionably the exciting cause of the tuberculosis. In nearly every instance this assumption is not susceptible of proof. I shall go into the subject of tuberculosis and industrial dusts more in detail in another place.

In studying the effects of dust on the health of the workers, the following factors must be kept in mind: (1) The type of dust; (2) The trade process followed by the worker; (3) The sanitary history of the worker, both personal and in the home.

Type of Dust

That dust is of very varied constitution is well known. First, it may be divided into two main parts, namely—inorganic and organic. The former may be farther subdivided into metallic and non-metallic, while the latter is distinguishable into animal and vegetable. To these two main divisions Hirt (15) added a third, namely —mixed dust.

Inorganic Dust

The inorganic dusts vary greatly in their physical characters; thus the particles may be acicular, or jagged in outline, or oval, or circular. The more jagged and angular the particles, the greater is their power of mischief. Another factor to be considered is the chemical composition of dust. Arlidge (16) has emphasized the importance of density and chemical composition. For instance, density is of great importance; and so is the degree of their divergence as regards organization and chemical constitution. Collis (1) has expressed the opinion that in general dusts appear to be more injurious as their chemical composition differs from that of the human body, or from the elements of which the body is normally composed. Thus it is seen in the case of lime dust (a normal constituent of the body) that notwithstanding its angular form, it is but a feeble irritant to lung tissue. Another example of comparative innocuousness of mineral dust is found in plaster of Paris in its native state. Although its particles have a square or rhomboidal form, with more or less acute angles, they have not the gritty hardness of silicious dust and diffuse readily through water.

In our own studies, cement dust, in spite of the enormous quantities inhaled, seems to be relatively harmless. This is probably due to the fact that it contains little or no silica.

Most of the recent studies on inorganic dust make it clear that metallic and siliceous dusts are the most potent causes of pulmonary fibrosis. The latter is by far the most important because more frequently encountered. The second report of the British Royal Commission on Metalliferous Mines and Quarries (1914) quotes experiments of Beattie as follows:

> "Certain mineral dusts, such as coal, clay, cement, were not shown by experiment to be injurious. Other dusts, e.g., silica, quartz, flint, sandstone, are injurious, as are also carborundum and emery. After careful consideration, therefore, we feel justified in concluding that, even although further investigation should disclose other dusts as injurious, the dust of fine crystalline silica is

especially injurious and is the more potent cause of fibrosis."

The commission was further of the opinion that inorganic dusts may be grouped in two classes:

(1) "Dusts, the inhalation of which has not so far been shown to be associated with any marked increased mortality from respiratory diseases—to this class belong coal, shale, slate, iron ore, clay, limestone, plaster of Paris, and cement." (2) "Dusts, the inhalation of which is associated with excessive mortality from respiratory diseases, and especially from phthisis—to this class belong quartz, quartzite (i.e., ganister and buhr stone), flint and sandstone."

It seems reasonably certain, from the evidence at hand, that hard, gritty dusts composed of sharp and jagged particles are the ones to be especially feared. The least innocuous of the inorganic dusts is soot. In most large cities and especially those containing large manufacturing plants, the air is filled with soot. Klotz (17) in a study of the lungs of individuals long resident in Pittsburgh, Pa., has shown that a mild grade of pneumoconiosis and fibrosis arises from this source.

The evil effects of metallic dust, usually in the form of fine particles of steel or iron, are frequently referred to and are cited by most writers as the most dangerous of all. It is noteworthy, however, that fine iron particles have rarely, if ever, been demonstrated in the substance of the lung. The cases of siderosis reported by Zenker (18) and Merkel (19) were caused by the red oxide of iron used by gold beaters and looking-glass polishers. The first case observed by Zenker was a girl who had inhaled a thick dust of iron for ten or twelve hours a day. Her work was to color blotting paper with a powder of red oxide of iron. Up to 1912, twenty-one cases of pneumoconiosis of this type had been reported (Dieulafoy).

Greenhow (20) in the examination of a grinder's lung, could find no excess of iron, either chemically or by the use of a magnet. In common with a number of other observers he was of the opinion that the pulmonary lesions were to be attributed to an excess of silica from the grindstone. Soper (21) in a chemical analysis of the dust from the New York subway showed that it contained 61.30 per cent. of iron, nearly all of which was in the metallic state; there was also 15.58 per cent. of silica. He points out, however, that it must not be supposed that the aggregate weight of metal which these figures indicate was capable of being mixed with the air which is breathed. Many of these iron particles were visible to the naked eye and too heavy and too large to be carried far or be sustained in the atmosphere, even by the strongest draughts of air.

The *size of the individual particles* plays an important part. The finer the dust the more dangerous, and there is every reason to believe that only the very finest particles obtain a permanent footing in the pulmonary tissue. Collis (1) lays special stress on the fineness of the dust, as in his opinion, it is only the very minute particles which gain access to the lungs. He states that all materials similar in origin and in chemical composition do not give rise to dust of similar fineness, and in this element of difference may lie the explanation of the fact that two otherwise similar dusts may produce dissimilar symptoms.

Several excellent studies have been made on the size of the silica particles found in the lungs. Watkins-Pitchford (22) states that the majority of visible siliceous particles (as detected by means of polarized light), in the sections of silicotic lung vary from 2 μ to 12 μ in maximum diameter. Larger particles seen by him in his investigation were found, not in the lung tissue, but in the cavities of bronchioles or alveoli. John McCrae (23) studied six lungs of miners who had suffered from silicosis. The ash from each lung was carefully dried at a low temperature so that no splintering of the silica particles should take place by excessive heating. A thin emulsion was then made from the powder and examined with the microscope. The great majority of the particles were found to be of indefinite shape and to have a diameter less than 1 μ (that is, a diameter less than one-eighth of that of a red blood corpuscle); the amount of material with a diameter less than 1 μ was very approximately 70 per cent. of the whole. Of the remaining 30 per cent. the longest diameter varied between 1 μ and 8.5 μ. Only a negligibly small number of particles was seen whose longest diameter exceeded 8.5 μ, and the very longest observed was 10.5 μ.

Watkins-Pitchford (24) found that the

prevailing outline of the particles (as shown by polarized light) was narrow and elongated with one or both extremities pointed; many showed a slight curve in their long diameter and some were elliptical; the commonest form was that of a very slender prism, having its ends cut off at a right angle or obliquely.

Concentration of the dust is also an important factor. If the worker is exposed to dust in a closely confined space the effects are more severe and pathological changes are more quickly produced than if the exposure occurs in a well-ventilated room or in the open. The very severe effects produced in the gold miners of South Africa and the zinc miners in southwestern Missouri are largely due to the fact that the rock dust accumulates in underground passages and chambers. In the Rand, holes are bored into the rock, which, if not moistened, emit a constant stream of fine dust which thoroughly impregnates the atmosphere; and, after blasting, sufficient time is not allowed to permit of the dust settling. The finest dust is produced by blasting; over 99.5 per cent. of the particles are below 12 μ in diameter and the average diameter is under 2.5 μ. This dust is produced in enormous quantities, although only over a short space of time. The dust contents of the air after blasting may amount to 500 mg. per cubic meter and contain in that volume nearly 86,000,000,000 particles of a diameter of 12 μ and downwards (25).

The length of exposure is also an important factor. It is rare, for instance, to find the appearance of definite early changes after exposure to siliceous dust with an exposure less than four or five years (Watt and Steuart). In the case of dusts less injurious, even early pulmonary changes may not be detected under ten or even fifteen years of exposure.

Briefly summarized, inorganic dusts, no matter what their source, produce definite changes in the lungs. They differ in the severity of the lesions produced in accordance with hardness, sharpness and chemical composition. At one end of the scale are the siliceous dusts, capable, under favorable conditions, of producing serious pulmonary damage in a comparatively brief period of time. At the other end are those which produce slight changes and then only after years of exposure. Among the latter may be mentioned plaster of Paris, lime, bituminous coal and soft carbonaceous material in the form of soot.

Organic Dust

Whether organic dust is of itself injurious is debatable. Certainly up to the present the evidence in favor of its causing chronic pathological changes in any way comparable to those produced by inorganic dust is not forthcoming.

The inorganic dusts are in part animal and in part vegetable. It is conceivable that a few of them, such as the dust arising from very hard wood, such as ebony or rose wood, may cause damage. And the same may be said of certain of the animal dusts such as ivory, bone, tortoise-shell, and horn. But even these stand very low in the list of injurious dusts and it is questionable whether the dust involved by working these substances is sufficiently fine to cause trouble.

Of the other organic dusts, some vegetable, others animal, which are encountered in the textile manufactures, there is no proof that they cause changes in the lungs. Among these dusts may be mentioned cotton, silk, wool, flax, hemp, hair, tobacco, etc. We have already seen that even the inorganic dusts vary tremendously in their power for mischief and that their injurious properties are largely dependent on hardness and on the angularity of the individual particles. If these properties are lacking the resultant injury to the respiratory tract is slight or even negligible, as in the case of soot or cement dust. Such being the case it is difficult to see how dust which is utterly devoid of these properties can of itself cause injury. As we shall show later, manufacturing processes associated with organic dust have in many instances been given a bad name because of the high incidence of tuberculosis among the employees. It has been assumed that the dust was responsible. This I disagree with and my reasons for this will be given in another place.

Oliver (26) is of the opinion that dust composed of cotton fibres is *per se* innocuous, and if the moisture necessary in the weaving of cotton could be dispensed with the trade would be harmless. On the other hand Collis (1) states that cotton "strippers" who are exposed to much cotton fibre

dust often develop, after some years of exposure, a condition in which the worker experiences asthmatic symptoms and sense of tightness across the chest, but that phthisis is not found to be especially prevalent among those affected. Oliver also is the authority for the statement that he had never seen any ill effects associated with the manufacture of cigars or cigarettes, at least in so far as dust is concerned. The experience of Dr. Miller and myself is in agreement with this.

In this study Drs. Miller and Smith have shown that the dust obtained from places associated with the organic type was never purely organic but a mixed form containing greater or smaller quantities of inorganic material. And even where the inorganic is present in noticeable quantities it is not sufficient to produce changes in the lungs which differ in any particular from those observed in the urban dweller. For instance, the investigation of a carpet manufactory revealed an appalling state of dustiness, and yet in spite of exposure for many years the roentgenologic pictures of the lungs showed changes which differ in no respect from those encountered in individuals who have lived all their lives in a large city.

This is in striking contrast to the changes observed among those exposed to inorganic dust. In these individuals the changes are definite and they show a steady development; so much so that, given the type of dust and the length of exposure, one can hazard a shrewd guess as to pulmonary changes as revealed by the roentgenograph.

If organic dusts are incapable of producing chronic inflammatory changes in the lungs, can they be wholly disregarded? In the light of our present knowledge this would be unwise. We need more and better studies in regard to this type of dust with reference especially to the part it plays as a carrier of bacteria. In order to do this intensive studies are needed. All contributing factors must be eliminated, and this is especially true in regard to tuberculosis. Faulty hygienic conditions in the shop; unsanitary living conditions; malnutrition and insufficient wages must be eliminated as factors.

Recent studies on the etiology of asthma point very clearly to the fact that the disease is, in many instances, apparently an evidence of protein hypersensitiveness. In many instances the evidence seems clear. Among the better known examples are instances in which an asthmatic attack is brought about by exposure to the emanations of animals or the inhalation of dust containing pollen. The condition is analogous to that produced in animals by the injection of a foreign protein and is characterized by spasm and constriction of the finer bronchioles and, to a lesser extent, by swelling of the mucous membrane of the bronchioles.

In several occupations associated with organic dust, acute respiratory symptoms often arise in susceptible individuals which are probably the result of protein poisoning. Oliver (27) states that in the manufacture of shoddy the grinding of the rags by machinery results in the formation of considerable quantities of dust, the inhalation of which is very trying to new hands but which has little or no immediate effects on the older work people. Those persons who are new to the trade develop what is known as "shoddy fever," the symptoms of which are a rise in temperature, severe headache, signs of bronchial catarrh, and running at the nose. The work people shiver as if they were going to have a severe fever and they complain of muscular pains. The condition is sometimes referred to as "mill fever" and has been noted as occurring in cotton operatives and those who work in flock, jute and flax. A similar condition is observed in grain threshers. Workers who are especially susceptible will, in the beginning of the threshing season, develop a headache and great irritation of the respiratory tract. In addition there is considerable depression, a sensation of chilliness and often high fever. After a few days these symptoms pass off and the worker is apparently immunized for the remainder of the season. The symptoms in this instance are probably due to the inhalation of pollen, especially that of rag-weed. Landis (28) and Bowen (29) have also directed attention to the symptoms arising in threshers. The symptoms, they state, are often severe and alarming. They consist of a chill, vomiting, a flushed face, delirium, and a temperature which may reach 104°F. There is marked congestion of the mucous membrane of the respiratory tract and a copious nasal and bronchial exudate which

contains quantities of microscopic dust particles.

In this category may be placed those instances of respiratory infections due to the inhalation of grain dust. While this dust contains much organic material it also undoubtedly contains considerable inorganic matter and is therefore to be regarded as a mixed dust. Formerly when the grain was transferred from vessels and cars to the elevator, and vice versa, the work was done by shoveling. Thomas F. Rochester (30) called attention to the fact that the "scoopers" or "shovelers" were extremely susceptible to acute respiratory disorders. Beginners often developed marked nasal irritation or a bronchitis, subacute in character. After two or three years an unusual type of broncho-pneumonia was of frequent occurrence. Because of the character of the employment it was commonly referred to in Buffalo as "elevator pneumonia." The attack was usually severe and at autopsy the lungs presented an engorged appearance at the bases and occasionally deep blood-red infarctions were found. The bronchial mucous membrane was without exception swollen and thickened. Convalescence in these cases was usually prolonged, being rarely under three months. A change of occupation was usually followed by complete restoration of health. The introduction of machinery for transferring the grain has apparently done away with the trouble.

Ramazzini, in 1670, in writing of the dust exposure in grain handlers, stated that: "The throat, the lungs, and the eyes sustain no small damage by it, for it stuffs and dries up the throat; it lines the pulmonary vessels with a dusty matter that causes a dry and obstinate cough." The acute symptoms in these cases are in all probability to be attributed to protein intoxication. In those who develop the evidences of organic changes in the lungs the condition can, without much doubt, be attributed to the large quantities of inorganic dust which is mixed with the grain.

Occasionally one of the acute infectious diseases is acquired by the inhalation of dust containing the specific organism. Rarely a fulminant and very fatal type of anthrax is encountered in which the disease is localized in the lungs.

The influence exerted by the trade process and the hygienic habits of the worker in his home are dealt with under the heading "The Relationship Between the Dusty Trades and Tuberculosis."

The Relationship Between the Dusty Trades and Tuberculosis

The most serious indictment against the dusty trades is that they cause, or at least predispose to, a high death rate from pulmonary tuberculosis. At first sight the evidence seems conclusive, but on closer analysis it is a question as to whether the facts as presented are altogether acceptable.

In considering the relation between the dusts and tuberculosis it is necessary to consider the inorganic and the organic type separately.

Inorganic Dust

Inorganic dust does produce definite pathological changes in the lungs. Of this there is no question. As has already been pointed out the changes may be very severe as in the case of silica, or they practically may be negligible, as in the case of soot. Because changes are produced by inorganic dust, the majority of writers on the subject assume that these changes render the individual more susceptible to tuberculosis. When we come to study the pathology of pneumoconiosis and tuberculosis, however, it is difficult to accept this view. The essential feature of the changes in pneumoconiosis is the formation of fibroid tissue. The arrest of a tuberculosis process, on the other hand, is brought about by the formation of fibroid tissue which walls off and prevents the spread of the tubercles.

In pulmonary tuberculosis the rapidity or the slowness of the spread of the disease is largely dependent on one factor, namely, the formation of fibroid tissue. In the acute forms of tuberculosis one of the striking features of the pathological picture is the absence of fibroid tissue. Caseous areas coalesce, break down, and form ragged, ill-defined cavities with apparently no attempt on the part of the cells to limit the spread of the disease. On the other hand, in the slowly progressing form of chronic ulcerative tuberculosis, and es-

pecially in the so-called fibroid phthisis, there is always an overgrowth of fibroid tissue. If cavities are present there is a well-defined fibrous wall, and scattered throughout the invaded portion of the lung the evidence of fibroid tissue is plainly apparent.

In the section on "Pathology" reference has been made to the presence, in silicotic lungs, of areas of dense fibrous tissue which sometimes show the presence of tubercle bacilli histologically, or if emulsified and injected into guinea pigs, tuberculosis sometimes develops. This, I take it, is an evidence of extreme resistance on the part of the lung rather than susceptibility to the infection. It has furthermore been pointed out that when tuberculosis develops in the early stage of silicosis that the tuberculous foci hasten the formation of fibrous tissue in their vicinity and that the silicosis or fibrosis in these areas is far in advance of that in other portions of the lung.

Beattie (31), in considering the occurrence of tuberculosis among grinders, feels that dust does its damage only in "reducing the area of effective lung tissue, and probably therefore encouraging the lodgment of tubercle bacilli, but no one who has studied the pathological processes in the lung in cases of tuberculosis can be anything but skeptical when he is told that fibrosis encourages the spread of the tuberculous process."

Under the circumstances it is difficult to understand how a process which, in one case retards the activities of the tubercle bacillus, can under other circumstances render the condition for its spread more favorable. Wainwright and Nichols (32), in their study of anthracosis, expressed the belief that coal miners were less susceptible to tuberculosis than other individuals because of the diffuse fibroid changes in their lungs. That the carbon dust was in any way germicidal they did not believe. Klotz (17) and Smart (33) have expressed the same opinion.

In the older literature on tuberculosis there are not a few references on the value of lime dust in the treatment of tuberculous individuals. In the past decade Fisac (34) has, on several occasions, drawn attention to the immunity against tuberculosis displayed by persons whose occupation brings them into close contact with lime and plaster. It is his belief that each individual soil has its special chemical composition. This chemical composition will decide whether tubercle bacilli can get a foothold and multiply or whether the tissues react with a fibrous growth, checking the proliferation of the germs.

Another stumbling block in the case of inorganic dust is that it leads to changes in the lungs which are not to be distinguished from tuberculosis either by the symptoms or the physical signs; and even the roentgenogram may, at times, be difficult to interpret. My own experience with potters under my care at the White Haven Sanatorium is that a diagnosis of tuberculosis is often made when in reality the individual is suffering from a diffuse fibrosis of the lungs, associated with dilatation of the bronchi. The only certain means of distinguishing between the two conditions is the examination of the sputum. It is not safe to assume that because an individual in a dusty trade has the symptoms and physical signs of pulmonary tuberculosis that he is necessarily tuberculous. The strongest evidence in support of the frequency of tuberculosis due to or associated with inorganic dust are mortality statistics. Unfortunately much of the value of this data is vitiated by careless diagnoses. Far too often a diagnosis of tuberculosis is made without a sputum examination.

Furthermore, I now have knowledge of several potters who became tuberculous, had their disease arrested, and returned to their former work. In each case a number of years have elapsed and the patient has remained well in spite of being exposed to the same conditions as existed prior to his illness.

It is not to be understood that tuberculosis cannot develop in the presence of an existing fibrosis of the lungs. It undoubtedly does. But when it occurs, and this is true of potters, it commonly runs a latent and more prolonged course than is the case of uncomplicated phthisis.

It has long been recognized that the age period at which potters succumb to tuberculosis is far beyond the average, and in addition the disease seems to be much less severe than the same amount of damage produces in other classes of patients. Most of the available statistics on the subject support this view. Thus the English mor-

tality statistics for the three years ending 1902 (35) state that the mortality of potters, between the ages of 20 and 35 years, falls below that of occupied and retired males generally. At every other period, however, it shows an excess which amounts to no less than 74 per cent. at ages 45 to 55 years, and to 66 per cent. at ages 55 to 65 years. The principal excess falls under the head of respiratory diseases.

The following table (36) shows the proportionate mortality from consumption among potters, compared with that of males in the registration area in the United States:

Age at Death	Deaths of Potters, 1897 to 1906, from		Per Cent of Deaths Due to Tuberculosis Among	
	All Causes	Pulmonary Tuberculosis	Potters	Males in Registration Area, 1900-1906
15 to 24 years	46	11	23.9	27.8
25 to 34 years	68	36	52.9	31.3
35 to 44 years	84	37	44.0	23.6
45 to 54 years	78	22	28.2	15.0
55 to 64 years	72	14	19.4	8.1
65 years or over	36	7	19.4	2.7
Total	384	127	31.3	18.0

My own belief is that the higher incidence of tuberculosis among those exposed to inorganic dust is due to the fact that the dust acts as a convenient carrier of tubercle bacilli. In other words, it is not the preliminary injury which the dust is responsible for that predisposes the individual to tuberculosis, but the readiness with which tubercle bacilli may be carried into the respiratory tract by a dust-laden atmosphere. If an infected worker is careless in spitting on the floor, the sputum becomes dry and mixes with the dust, thus making it easier for the bacilli to reach the lung. Moreover, tubercle bacilli which become mixed with dust are, to a certain extent, protected and not as much exposed to the germicidal action of air and light as are those deposited in places free from dust.

In a survey made of the conditions in the gold mines in the Transvaal, South Africa, Watkins-Pitchford (37) found that 15.2 per cent. of samples of sputa obtained underground, chiefly from shafts and main traveling ways, showed the presence of tubercle bacilli, as against 2.5 per cent. of sputa collected in the living rooms or places of resort of white and native mine workers on the surface. The difference in these figures is probably to be ascribed to the fact that the dark, humid atmosphere of the mine aids in prolonging the life of the bacillus. It was also observed that the tubercle bacillus will survive in acid mine waters for a period of at least two months. If, therefore, a number of tuberculous infected miners are careless in spitting about the working places in the mine, the chance of infecting their fellow-workmen is great. And this danger of infection is quite independent of whether the workers have developed silicosis or not.

Beattie (31) has expressed the belief that the prevalence of tuberculosis among grinders is due to spitting on the wheels and hands, and thus contaminating the water which all use for wet grinding.

In a preliminary inquiry into the prevalence of pulmonary tuberculosis among the native mine workers in the Rand, Watkins-Pitchford, Orenstein and Steuart (38) state that tuberculosis is the main incapacitating factor in silicosis and that if open communicable cases of tuberculosis are rigidly excluded from the mines, the danger is greatly reduced.

Another factor to be considered is the exposure to infection entirely independ-

ently of the occupation. Tuberculosis has long been recognized as a house disease, for it is here that exposure occurs more often and more intensely than anywhere else. In an intensive study of 743 garment makers made by Reed and myself (39), tuberculosis in other members of the family was encountered in 27, or 6.7 per cent. of 402 males, and 13, or 3.8 per cent. of 341 females. The question of whether the worker is exposed to the disease in the home or has a family history of tuberculosis is extremely important. When such is the case it would be difficult to fasten the blame on the occupation. During the year 1913 there were treated in the Phipps Institute Dispensary 685 cases with a positive diagnosis of tuberculosis, and of this number ninety-six, or 14 per cent. were garment-workers. Twenty-seven, or 28 per cent., of the ninety-six, gave a family history of tuberculosis. Furthermore, the social histories of patients with tuberculosis but following an occupation other than that of garment making, showed that in 108 instances one or more members of the family were employed as garment-makers. It is thus seen that the worker is often exposed to danger of infection in the home.

In the present investigation the family histories of thirty-nine potters showed that the mother or a brother or a sister had died of tuberculosis in six instances (15.4 per cent.). In four more it was stated that the father had died of "potter's asthma," which might or might not have been tuberculosis.

Lanza (40) has emphasized the poor and often wretched conditions under which many of the zinc miners live. Unhygienic living conditions, carelessness of the miners themselves, and overcrowding in small three and four-room shacks are of frequent occurrence. In common with the South African observers, he found little tuberculous infection among the women which could be attributed to the men. Lanza believes, however, that this danger has been underestimated, although the condition may be explainable by reason of the short period during which many cases of miners' consumption emit tubercle bacilli before death. The danger to the children on the other hand is, he believes, a serious one. He concludes that aside from the hygienic supervision of working conditions underground, education of the miner against the spread of infection and supervision of miners' children, especially those of consumptive parents, are matters of vital importance.

In this connection it is interesting to note that in the state of Victoria, Australia, statistics show that while the incidence of tuberculosis is excessive among males in the Bendigo mining district, it is also excessive among the females who are in no way involved in mining operations. A careful study of sixty-five miners showed that 50 per cent. gave a clear history of close contact with cases of tuberculosis (41).

In closing this subject, I would redirect attention to Cornet's (42) original observations on the transmission of tuberculosis, namely, *The Diffusion of Tubercle Bacilli Exterior to the Body* and *The Mortality of the Nursing Orders.* An excellent review of both papers will be found in Tyndall's *New Fragments,* Appleton & Co., 1897. It has seemed to me, and the conviction grows stronger the more I study the problem, that the universal tendency is to emphasize the danger of dust and to minimize the fact that without the tubercle bacillus tuberculosis cannot be produced. Whether intentional or not, one gets the impression in reading of the dangers of dust that it is the dust which produces tuberculosis.

In a few instances conditions simulating pulmonary tuberculosis can be produced by dust, but in the overwhelming majority of cases no such change occurs. In other words we can eliminate dust, at least in the industrial sense, and still be exposed to the danger of tuberculosis if open active cases expectorate freely about the working places. Cornet showed from his study of the Catholic Nursing Orders in Germany that the mortality from tuberculosis was appallingly high and was to be ascribed to the close confinement of the nurses and to carelessness on the part of patients at a time when the danger of tuberculous sputum was but little appreciated. Let us keep before us the fact that some of the inorganic dusts are, *per se,* capable of producing serious pathological changes in the lungs; that others lead to slight changes; and that many of them produce no appreciable alterations whatever. Tuberculosis may be grafted on

such a process, but in such an event the exciting cause is the tubercle bacillus which has been thrown off by a pre-existing case of tuberculosis. In this connection may be quoted a paragraph from the second report of the British Royal Commission on Metalliferous Mines and Quarries (1914): "One conclusion at which we have arrived is that the cause of miners' phthisis is the inhalation of dust of crystalline silica, upon which is superimposed tubercular infection. Moreover, we agree that it is the tubercle bacillus which causes destruction of the lung and that dust is not necessarily dangerous to life." Professor Beattie said "The dust is not nearly as dangerous to life as the tubercle bacillus. If you get rid of the bacillus of tuberculosis the dust is not so bad."

Organic Dust

In the case of organic dust the problem is decidedly different. In the first place we can dismiss at once the question of injury to the respiratory tract as the result of the inhalation of organic material. The only factor in common is the part played by the dust particles as carriers of tubercle bacilli.

There is no doubt that among those who are employed in trades in which there is an exposure to organic dust there is often a high death rate from pulmonary tuberculosis. That organic dust *per se* is responsible, in that it produces pathological changes in the lungs, and thus renders them more susceptible to tuberculous infection, cannot be demonstrated. There is no pathological proof that such is the case and our experience with the X-rays is distinctly adverse to such an opinion.

In the case of inorganic dust the proof is indubitable and if undue exposure to this type of dust occurs, pathological changes are seen to result no matter what the habits or circumstances of the individual may be. Among those exposed to organic dust there are a number of factors to be considered in determining the high incidence of tuberculosis in this class of workers.

In the first place a large proportion of workers exposed to inorganic dust such as potters, miners, metal workers, are skilled and highly paid artisans while those employed as cotton mill operators, textile workers, etc., are, for the most part, unskilled and poorly paid. The relationship which exists between wages and ill-health is one of the most debated questions of the day. To what extent higher wages would do away with disease is problematical but there can be no doubt that a low wage often compels the worker to live in localities, the sanitary conditions of which are often poor. Furthermore, he is only too frequently undernourished, either because of an inferior quality of food or insufficient food. In this connection, however, it is only fair to state that the undernourished condition of many of the laboring class is to be ascribed to ignorance as to food values. In an intensive study made of the dietary of dispensary patients, many of them employed in the textile trades, Craig and I (43), found that they were getting only about four-fifths the quantity of food they should. This was due in part to an inadequate wage and in part to ignorance of food values. Formerly the working environment was often unsanitary, but in recent years tremendous strides have been made in the direction of improving these conditions.

In nearly all of the occupations in which the worker is exposed to organic dust it is well to remember that in the badly ventilated state of one factory compared with another, the home life and surroundings of the work people, poverty, heredity, age and sex are to be found conditions that favor the production of ill-health, and are therefore not to be ignored. This can best be illustrated by a few concrete instances. It is well known that the mortality from tuberculosis among tobacco workers is excessively high. This trade is usually listed as one of the dusty trades. Two years ago there were admitted to the White Haven Sanatorium, White Haven, Pa., a number of patients from one of the counties in an adjoining state. Among this number were ten young women who gave as their occupation that of cigar maker. All were suffering from a moderately advanced stage of tuberculosis. These women were foreign born, mentally stupid, untidy and of the type that made it reasonably certain that their living conditions were far from being good. They all came from a group of small manufacturing towns closely adjoining each other. These towns are built on a marsh, the

streets are, as a rule, unpaved, underdrainage is lacking, and as a personal inspection showed, the living conditions were vile. There was but one visiting nurse, and she informed me that the enforcement of cleanliness among these people was almost impossible. In addition to their ignorance of hygiene a low wage forced them into the meanest quarters and in addition rendered an adequate diet impossible. That is one side of the picture.

The other side consists of the cigar factory in which these women were employed. It was modern, well lighted, well ventilated and the reverse of being overcrowded by workers. As I had never personally inspected a cigar factory I accepted the dictum that this trade was a dusty one. There was little dust of any kind and so far as tobacco dust is concerned there was none at all for the following reason. In as much as the tobacco leaves are very fragile and must be handled and manipulated constantly in manufacturing the cigar, it is apparent that this can be done only by keeping them moist and pliable. How quickly a dried out cigar can be crumbled into dust is familiar to all. Tobacco dust is absent from this industry, therefore, because of economic reasons.

Dr. E. H. Funk who inspected several large cigar factories for me noted the absence of tobacco dust. Smith and Miller (44), in a hygienic survey of forty-eight cigar manufacturing establishments in Philadelphia concluded that cigar making is not necessarily a dangerous industry. Certainly so far as tobacco dust is concerned it is not. In common with many other manufacturing plants, many cigar making establishments contain varying amounts of mixed dust which is carried in on the shoes of the workers or sifts in through the windows. This is often allowed to accumulate for months at a time. Among the cigar makers whom we studied roentgenologically, none of them showed changes in the lungs which differed in any way from those of the city dweller and in some instances they had followed the trade for twenty-five years or more.

Another fallacy regarding the possible effect that dust may have on ill-health is the failure of our statistics to separate the various occupations into trade processes.

A man employed in a felt hat factory, for instance, will almost invariably designate his employment as a "hatter." It is to be borne in mind, however, that there is a wide difference in the character of the different processes concerned in the manufacture of a hat. Those handling the raw fur which composes the felt may, if exhausts are not employed, be exposed to dust. On the other hand, those who mold the felt into form are as far removed from dust as possible as they work in a steam saturated atmosphere. While this industry is often included among the dusty trades it is noteworthy that of the hatters we have seen at the Phipps Institute, all have been from the molding department. If tuberculosis is unduly prevalent among the workers in this process it is to be ascribed to catarrhal changes induced by exposure to sudden changes in the temperature and to the dampness. Dust certainly plays a very small part.

The cause and effect in the case of inorganic dust is direct and apparent. In the case of organic dust, however, there are a number of contributing factors to be considered and unless we have a complete picture of the worker's life it is unsafe to ascribe all the ills to which the worker may be heir, to the nature of his occupation.

This was well brought out in an intensive study of 743 garment workers made by Reed and myself (39). In this study it was shown that among those workers who took their meals irregularly or who had insufficient or inadequate food and among those who did not get sufficient sleep the incidence of tuberculosis was much higher than in the case of those leading a regular life and obtaining sufficient nourishment. Among the women who were getting insufficient food and sleep the incidence of tuberculosis was three times that of those of whom the reverse was true.

As in the case of inorganic dust, the undue incidence of tuberculosis in association with organic dust is to be explained by the presence of infected individuals who are careless in expectorating on the floors of workrooms and thus permitting the tubercle bacilli to become mixed with the dust.

PATHOLOGY

Inorganic Dust

Before taking up the successive changes which are produced by the inhalation of dust, attention should be directed to the fact that the air passages are provided with a natural defensive mechanism against the entrance of foreign material. The average amount of air which a healthy grown person takes in at each breath has been estimated to be about one-half a litre (about 30 cubic inches). Now there is being little air breathed by the great mass of people, and especially by city dwellers, which does not contain particles of dust and bacteria of various sorts. In an analysis of the outdoor air from various parts of New York City, Prudden (45), found that the average number of bacteria in 10 litres to be 376, and of moulds six.

In buildings and in private houses the number of dust particles and bacteria is greatly reduced. It has long been recognized that the solid particles which we breathe in with the air either through the nose or mouth do not come out with the expired air but are retained on the moist surface upon which the air impinges, going in and coming out. Straus in one experiment found that the expired air contained only forty bacteria, whereas the inspired air held over twenty thousand. Not only bacteria but dust particles are caught largely in the nose, or mouth or upper pharynx. The nose especially is a very efficient dust filter and many dust particles are held on the moist surface of its mucous membrane. When the air current leaves the nose it turns downwards and impinges against the posterior wall of the pharynx. Much of the dust is arrested at this point. The mouth is not so well adapted as the nose for moistening the air and removing the dust particles and bacteria. For this reason those who suffer from nasal obstruction or who breath through the mouth from other causes are more susceptible to "colds" than those who breathe through the nose. A very considerable proportion of the dust in the inbreathed air is spat out, swallowed or removed from the nose.

According to the experience of Watt, Irvine, Johnson and Steuart (25), silicosis is more apt to develop in a mouth breather than in a nose breather. In our own investigation we were at a loss to explain the variations noted in those exposed to the same kind of dust and for an equal length of time. This difference in resistance of individuals to dust was also noted by Arlidge (46), many years ago. Some workers will show in their lungs marked pathological changes while others will show very little evidence of damage, although the circumstances are identical in both. Thinking that variations in the upper respiratory tract might explain the matter, Dr. George Fetterolf, at our request, examined the nose and throat of a number of cement workers. He was unable to find anything, however, which threw any light on the matter. There can be no doubt, however, that the mechanical defense in the nose is superior to that of the mouth and that mouth breathers are therefore more susceptible. On the other hand, there seems to be no doubt that individuals vary almost as much in their reaction to inert dust particles as they do to bacteria. For instance, a potter whom we have had under observation was exposed to clay and flint dust for nearly forty years and yet his lungs showed but a moderate grade of pneumoconiosis. On the other hand, many of his fellow workmen equally exposed and in some instances less so, showed extreme fibroid changes.

Let us return, however, to the dust particles. The floating material which is carried past the upper defenses enters the trachea and bronchi and lodges in their moist walls. Nowhere in the body has nature provided a more ingenuous arrangement for expelling unwelcome intruders. Completely lining the larger air tubes like a mosaic, are myriads of tiny cells shaped something like a narrow short club and set upon end side by side. Projecting from the free ends of each one of these cells is a number of minute hairs. These cells are called cilia. "These myriads of cilia, year in and year out, day and night, while life lasts, are constantly swinging their free ends back and forth, bending as they recover, and then with a quick snap forward so that any small object which lodges on the walls of the larger air tubes—since all the cilia act in rhythm—is swept upwards toward the mouth, away from the perilously delicate and

sensitive lungs." (Prudden).

By the action of the cilia the bulk of the dust particles is arrested and removed under ordinary conditions.

The particles which escape the cilia and penetrate deeper into the respiratory tract encounter another defensive force, namely, the phagocytes and the large cells lining the alveoli. These alveolar cells have been termed the normal "respiratory scavengers." Some of the dust particles are taken up and retained by the large cells lining the alveoli; others are seized by the phagocytes. In the case of bacteria the phagocytes destroy them by absorbing and digesting them. In the case of inert dust particles they are either expelled in the secretions or carried to some point where they will do the least damage. But even these fail to deal with all the dust particles and when overwhelmed as in great exposure, the particles penetrate the mucosa and reach the lymph spaces.

The last defense is the lymphatic system of the lungs and pleura. The lymphatic system of the lungs consists of a series of irregular, narrow channels which open into larger and still larger trunks. The terminus of this system is formed by the bronchial lymph nodes. An interesting observation regarding the direction of the lymph flow in the lungs has been made by Dunham (47). By means of large serial sections he has shown the presence, in the lymph vessels, of valves pointing definitely toward the pleura. These lymphatic vessels have their origin in some instances, in the interalveolar spaces and accompany the large vascular trunks and the bronchi toward the root of the lung; in other instances, they originate in the sub-pleural spaces and communicate on one side with the pleural cavity and on the other anastomose with the lobular and interlobular lymphatics. Many dust particles are taken up by these vessels and deposited in the lymphatic filters, the lymph nodes.

In spite of these defenses, however, there accumulates in the pulmonary tissues a considerable amount of foreign material. The amount will depend almost entirely on the degree of exposure. In all urban dwellers who reach adult life there is some evidence of dust accumulation in the lungs. At birth the lungs are of a pink color but as time goes on and the dust particles gradually accumulate, principally in the form of carbonaceous material, the lungs assume the familiar greyish color seen at the autopsy table. Pneumoconiosis of this degree produces but slight organic changes and rarely interferes with health.

While all forms of inorganic dust bring about essentially the same change in the respiratory tract, they vary one from another, in the extent of the lesions produced and the severity of the symptoms. The sharper and more angular the dust particles, the greater will be the amount of mechanical injury and hence the greater the inflammatory reaction. The most dangerous of the inorganic dusts is the siliceous.

If exposure to the dust is sufficiently long there develops a pharyngitis and later a bronchitis. Between simple irritation as the result of brief exposure, and extensive tissue changes, as the result of prolonged exposure, varying degrees of pathological alteration may occur. It is noteworthy that the changes are very slow in their evolution and except under extraordinary circumstances, it takes years to bring about serious damage.

In the case of a worker exposed to unusual quantities of inorganic dust the majority of the particles are, for a varying length of time, arrested by the moist surface of the mucous membrane, by the action of the ciliated epithelium and by the phagocytes. Sooner or later, however, these defensive forces weaken and finally the dust passes into the lymph channels and also along the finer bronchi until it reaches the parenchyma of the lungs. As a foreign substance it then sets up a chronic inflammatory process.

Our experience is in agreement with that of Arlidge (48) and Watt, Irvine, Johnson and Steuart (25) in that the anterior and inferior marginal portions of the lungs, where expansion is most free, are always less affected than the posterior and apical portions. Radiographic evidence shows also that the change is frequently slightly more advanced in the right lung than in the left.

The microscopic changes which occur in pneumoconiosis have been described by Wainwright and Nichols (32), Haythorn (49), Klotz (17), and by Watt, Irvine, Johnson and Steuart (25). The

evolution of pneumoconiosis is characterized by several well defined stages:

(1) The very earliest changes have been well described by Wainwright and Nichols who, because of accidental deaths, were able to study the lungs of men who had worked in a coal mine but a few months. In these cases they found that some of the epithelial cells lining the alveoli had become swollen and contained particles of coal dust. Sometimes a few larger desquamated cells containing much pigment are found in the alveoli lying loose with some detritus and free dust particles. Even in this early stage, dust particles are seen in the walls of the air vesicles and around the small bronchi. In this stage there is no evidence of connective tissue proliferation. In the case of silicosis, however, it is likely that fibrosis begins at an earlier period than is the case in anthracosis owing to the more irritating properties of the silicious dust.

(2) In this stage it is evident that the dust particles have penetrated all of the first defenses and have gained entrance to the lymphatic channels. The swollen cells containing dust particles are much more numerous and in addition there are present large mononuclear phagocytes filled with dust particles. They lodge first mainly in the small aggregations of lymphoid tissue which lie between the alveoli and along the course of the perivascular, peribronchial and interlobular lymphatics. In a microscopic study of seven silicotic lungs, Watkins-Pitchford (24) was able to demonstrate the situation, outline and dimensions of the mineral particles by means of polarized light. Watt, Irvine, Johnson and Steuart (25) describe the stage as one of *discrete fine fibrosis* which results from the aggregation of dust particles along the course of the small blood vessels and bronchioles and to a limited extent in the interalveolar, interlobular, and sub-pleural tissues. The fibrosis at this stage is almost entirely perivascular and peribronchial. The alveolar walls generally are not thickened and the alveoli are not reduced in size, although they show a certain amount of catarrh.

(3) In this stage the accumulations of dust particles gradually increase. The early perivascular and peribronchial fibrosis becomes more accentuated and in the interalveolar, interlobar and sub-pleural tissues become thickened. In addition nodular collections appear at the points of junction of the various lymph channels where small receptaculi are formed. These nodules become so prominent that they are readily felt by the finger and at times the course of the lymph channel can be detected by the sensation of touch. At the points where the dust collects the fibrous tissue is arranged in concentric layers, and toward the periphery the dust particles are especially numerous. The fibrous masses are well seen in the septa that run in from the pleura. In places considerable sized black triangles with their bases on the pleura are seen, showing where the septum has been completely filled up with dust. The striking point in the whole picture is the extensive plugging and obliteration of the small and medium-sized lymphatics and the compression of the large ones. In the pleura and the peribronchial lymph nodes the picture is a similar one (Haythorn). In this stage the bronchial and mediastinal lymph nodes become enlarged. By some, the plugging of the lymphatic vessels is considered as predisposing the individual to lobar pneumonia. Klotz leans to this view as the result of his studies. Although pneumonia prevails to a considerable extent among the "blacks" in the Rand mines, those who have studied the subject state that silicosis seems to exert little influence. The new arrivals seem especially prone to develop pneumonia but after a residence of six months the incidence of this disease is no greater among the black than among the white miners.

(4) The final and advanced stage is characterized by a general nodular dissemination throughout both lungs. In many places the nodules coalesce forming large fibrous areas. These advanced changes take place as a rule only after years of exposure.

(5) A most important change, from the view point of prevention, was noted by Wainwright and Nichols. They found that in the case of individuals who had formerly been coal miners, but who for many years had not followed that occupation, the lungs no longer showed signs of irritation. The swollen epithelium had subsided and again become normal, and neither the cells nor the alveoli contained

dust. The deposits of dust in the alveolar walls, the septa and peribronchial tissue, however, still remained, as did also the connective tissue thickening.

The changes described above as occurring in man have also been produced in animals. Beattie in an experimental study with guinea pigs drew the following conclusions:

(1) That the effects produced in the lungs of guinea pigs which have been exposed to the inhalation of dust correspond with those produced in man. (2) That the effects produced vary with the length of exposure and particularly with the quantity and quality of the dust which is inhaled. (3) The more concentrated the dust in the atmosphere the more rapidly will fibrosis be produced and the more irritating the dust the more intense will be the fibrosis. (4) The inhalation of such stone dusts as are rich in silica seems to be particularly injurious, and (5) that the powdered shale used in these experiments does not produce more irritation in the lungs than does coal dust, and judging by the comparatively non-injurious effects of coal dust and the general health of the workers, powdered shale may also be regarded as comparatively harmless.

In a study of the lungs of rats exposed to dust in gold mines in the Rand, Johnson (25) states that the development of silicosis in these animals very closely resembles that which occurs in man. The condition is definitely progressive and can be subdivided into stages similar to those noted in miners.

Gross Anatomy

The color of the lung which contains dust pigment will vary according to the extent of the pneumoconiosis and the character of the dust. It may be of varying shades of gray, intensely black (anthracosis) or it may be red, as in the cases of siderosis due to the red oxide of iron reported by Zenker. The slate gray color of the lungs of the city dweller is familiar to all. This constitutes the early change in pneumoconiosis. In the absence of any other lesion such lungs are regarded as normal. Even in the stage of discrete fine fibrosis the lung shows no gross change although occasionally "precocious" macroscopic nodules are noted and the smaller vessels and bronchioles may be slightly raised above the cut surface and definitely palpable.

When the fibrosis reaches a more advanced stage the mottling on the surface of the lung is quite distinct and the interlobular septa are readily distinguished. Occasionally the surface of the lung is scarred and distorted. On palpating such a lung it is aerated throughout but is distinctly less elastic than normal. The walls of the small blood vessels and bronchi are seen to be thickened and they stand out distinctly on the cut surface. Pigmented areas are also seen and it is common to find a number of small microscopic fibrous nodules under the pleura or in the substance of the lung. The bronchial lymph nodes are fibroid and deeply pigmented.

In the advanced stage the lung is hard and more or less solid as the result of fibrosis and is always heavier than normal. In a series of silicotic lungs Watkins-Pitchford (50) found that they weighed from two to three times that of the normal organ. This is due to some extent to the increase in the amount of fibrous tissue but largely to the deposition of dust. In those exposed to siliceous dust Kussmaul (51), found that after incinerating the lung the residual ash might constitute 40 or 50 per cent. of the total. Arlidge (52), in an analysis of the ash from a potter's lung found it contained 47.78 per cent. of silica.

The dominant feature is the fibrosis. The organ often cuts with some difficulty and gives a creaking sound owing to the presence of fibrous nodules. Grittiness, which is so often alluded to, is, in the experience of Watkins-Pitchford rarely present even in an advanced stage of silicosis. The cut surface feels rough and gritty, partly as a result of the thickened vessels and bronchi, and partly as the result of the deposit of mineral material. Massive fibrous areas may be seen. In some instances they are due to the coalescence of smaller areas, in others they are due to a chronic tuberculous invasion of the lung. In many instances the latter show no gross evidence of tuberculosis, but careful histological studies will often show a few tubercle bacilli and emulsions made from this tissue, if injected into a guinea pig, will often produce tuberculosis. Clinically it is quite likely that such lesions are so latent that they are innocuous. In cases of silicosis more than in any other form of pneumoconiosis the acute forms of tuberculosis, acute pneumonic phthisis and tuberculous broncho-pneumonia, are apt to develop. It has also been noted that when a tuberculous focus occurs in a silicotic lung it seems to hasten the advance-

ment of the silicosis and that about such an area the condition presents itself as a far advanced stage of silicosis while elsewhere the lung may appear to be only in the first stage of the disease. The dense fibrous areas containing a few tubercle bacilli probably represent a slight tuberculous focus which has been healed.

In advanced stages of pneumoconiosis the pleura is usually adherent to the chest wall, although the extent of the adhesions varies somewhat with the nature of the infecting dust. In anthracosis the adhesions may be very slight while in silicosis they are usually dense, the lung being adherent not only to the chest walls but to portions of the pericardium. In quartz miners Purdy (53) states that a common finding is an old or recent pleurisy; notably in the locality of the fifth and sixth ribs in the axillary region.

The only other condition likely to give rise to such extensive pleural thickening is chronic tuberculosis. In the case of the latter disease the lung is shrunken, ragged and collapsed which is in marked contrast to the full, firm and much weightier lung seen in pneumoconiosis.

In common with all forms of pulmonary fibrosis no matter what the exciting cause, dilatation of the bronchi is a common finding in the advanced stages of pneumoconiosis. Calvert Holland (1843) was the first to direct attention to this condition. The dilated bronchi are to be found, as a rule, in the portions of the lung which are most markedly fibroid, namely, about the roots and at the apices.

In common with other forms of chronic inflammation of the bronchi the walls may be thickened and hard. The mucous membrane may be of a dull red tint, or brownish in color, the discoloration being evenly distributed or occurring in patches. The membrane may be thickened in some places and in others thinner than normal. Very often the fine capillary vessels present a varicose appearance.

Emphysema located along the anterior margin and at the bases of the lungs is of frequent occurrence. Emphysema may be noted also between the areas of fibrous tissue.

Cavity formation, the result of tissue necrosis is not common in uncomplicated pneumoconiosis, although it does occasionally occur. Among zinc miners Lanza (40) states that necrosis as the result of pyogenic infection is not infrequent. This manifests itself clinically by the breaking down of the lung tissue and the expectoration of characteristic slaty blue sputum. Abscess formation in the lungs has also been noted among zinc miners. When a cavity is present it is to be regarded as being tuberculous in character until proved otherwise.

A not infrequent finding in anthracotic lungs is a pseudo-cavity due to a saccular dilatation of a bronchus. It is frequently located at the apex, and is readily distinguished as being of bronchial origin by the smooth wall which is continuous with that of the bronchus. Clinically it is important to keep in mind the fact that the bronchi are often dilated in the apical portion of the lung as the physical signs are not to be distinguished from those obtained in the case of a true cavity.

The diaphragm shows most interesting changes. In advanced cases it is nearly always distorted and its functional capacity greatly reduced. As fibrous changes first occur at the root of the lung and often extend downward, the phreno-pericardial angle is often obliterated comparatively early in the disease. This causes a restriction of the inner half of the leaflet usually most marked on the right side. In the advanced stage a sharp angulation of one or both leaflets is often seen, especially on inspiration. In many of these cases it is easy to demonstrate the presence of a fibrous strand extending from the hilus of the lung to the diaphragm at the angular point. This evidently anchors the diaphragm at this point and causes the leaflet to become peaked or angular on inspiration.

If the fibrosis is more decided on one side than on the other, the most affected side will show a greater amount of retraction and the heart will be displaced or drawn toward that side. In as much as pneumoconiosis generally produces a more or less uniform bilateral fibrosis, displacement of the heart is not a marked feature. In the terminal stages dilatation of the right heart is commonly present. It is caused by the obstruction in the pulmonary circulation as the result of the fibroid changes which have occurred in the lung.

Organic Dust: Morbid Anatomy

Although cotton fibers have been demonstrated frequently in the sputum of operatives in cotton mills the invasion of the lung by the material has not yet been shown. And this holds true for all forms of vegetable and animal fibre with the possible exception of particles of dust obtained from the abnormally hard woods.

References in the literature to pathological studies of the lungs of those who have been engaged in trades which have been associated with much dust of animal or vegetable source, are not of frequent occurrence. Or perhaps it would be more accurate to state that such studies rarely have been made with reference to the effects such dusts might have on the lungs. There can be no doubt that the lungs of such individuals have been studied but it is significant that but few references have been made to changes which are analogous to those encountered in the lungs of those exposed to inorganic dust.

Greenhow (20) for instance, studied several lungs obtained from flax dressers. These lungs grossly presented much the same appearance as those seen in potters or others engaged in work which causes exposure to inorganic dust. On incinerating them, however, it was found that the resulting ash was partially dissolved in boiling hydrochloric acid; the part left was dissolved by hydrofluoric acid, thus proving it to be silica.

Hirt (54), states that in two cases where the lungs of horse hair workers were indurated precisely like those of sandstone workers, he could find no trace of horse hair, and therefore concludes that the effect was probably due to the inorganic constituents of the dust.

In considering the effects of inorganic dust all the evidence points to the fact that even this type varies greatly in accordance with the size, hardness and regularity of the dust particles. In as much as all the vegetable and animal dusts with but few exceptions, are devoid of these characteristics it is difficult to understand how they could cause injury. When pathological changes are encountered in the lungs of those who have been exposed to organic dust the lesions are to be ascribed to inorganic material—in other words, it is a mixed dust.

Finally, it might be said that the roentgen rays reveal indubitable evidences of chronic pathological changes in the lungs of those exposed to inorganic dust; that these changes are definitely progressive and develop in a fixed sequence. On the other hand no such changes have been noted in the lungs of those exposed to organic material even when the exposure has been as long as thirty years.

SYMPTOMS

Inorganic Dust

Pathological changes due to an inert substance, such as inorganic dust, differ from those of bacterial origin in that they are slowly but definitely progressive so long as the exposure to the dust continues. Unlike the changes caused by bacteria there are no periods of quiescence and recrudescence. Furthermore, the changes are progressive only so long as the irritant is constantly operative; when the individual is no longer exposed the lesions become non-progressive, although those already present persist throughout life.

Exposure to any form of dust, even for a brief period of time, is apt to cause considerable irritation of the upper air passages, as manifested by a tickling sensation in the throat, cough and sometimes sneezing. After the worker becomes accustomed to the dust he may have no evidence of respiratory irritation for years. In other words, during the first stage of pneumoconiosis there may be no symptoms or only those indicative of a pharyngitis. Even in the early stages of the resulting fibrosis, symptoms may be slight or entirely wanting. This long period of latency is not to be wondered at in a condition whose pathological beginnings are fine and generalized. The symptoms will naturally be correspondingly insidious and their onset more elusive in character than is the case with most other pulmonary diseases. To this latency, in spite of definitely progressive lesions, is to be ascribed the difficulty of recognizing the condition by ordinary clinical methods. That the fibrosis is the principal cause of the respiratory symptoms there seems to be no doubt.

The more the effects of inorganic dust are studied the more apparent it becomes that silica is by far the most injurious

form encountered. When the worker is subjected to this type of dust in great concentration the fibroid changes in the lungs develop relatively quickly and evidences of respiratory damage are correspondingly early in their appearance. The evil effects of silicious dust have been well shown among the gold miners in South Africa and by Lanza (40) among the zinc miners in southwestern Missouri. In both instances the dust is almost entirely silicious in nature and, by reason of the work being done in closely confined underground chambers, the concentration is great. Under these circumstances early pulmonary changes may be noted in four or five years.

Even in the case of dusts which are not purely silicious the amount of damage seems to be proportionate to the amount of silica they contain. If silica is absent or exists in small amounts only, the evolution of the process is very slow and years may elapse without there being any appreciable damage. Thus among sixteen cement workers studied in the present investigation only one had a cough. The remainder were entirely free from respiratory symptoms. While the average length of time these men had been in the industry was comparatively short (average 10 years) the dust exposure was most intense. Among potters whom I have studied (55), serious symptoms rarely arose until the worker had been in the trade from ten to twenty years. In the present study freedom from any respiratory symptoms was noted after 38, 41, 49, 51, and 54 years of employment among thirty-nine potters. On the other hand, one man after six years in the trade had had an irritating cough for over a year.

The progress of the disease is, therefore, commonly slow but when induration of the pulmonary tissues has once been established, it tends to advance more rapidly, though insidiously. As a rule, *cough*, often unproductive in character, is the first symptom, especially in the milder types of pneumoconiosis. This is usually worse in the morning, is often paroxysmal, and tends to become increasingly severe. Following the morning paroxysm of coughing the worker frequently vomits. That eating seems to play some part in the vomiting is apparent by reason of the fact that the omission of breakfast minimizes or abolishes the paroxysm. By some the coughing paroxysm is ascribed to irritation of the gastro-intestinal tract as the result of the ingestion of the dust. Occasionally the cough may be wanting entirely. In the great majority of cases the dry, hacking cough is sooner or later associated with *sputum*. The expectorated matter at first is small in amount, tenacious and greyish in color as the result of small specks of carbonaceous matter. Even when the dust is not black in color, as in the case of clay or flint dust, the expectorated matter is usually greyish in color. In coal miners the expectorated matter is often inky black in color, hence the name "black-spit," sometimes applied to anthracosis. If the dust is composed of some distinctive coloring matter, such as red oxide or iron or ultra-marine blue, the sputum maybe either red or blue in color. Lanza (40) states that among zinc miners the sputum is often very characteristic, in fact diagnostic, being of a marked slaty blue color and of a very tenacious consistency. In doubtful cases sputum of this character is sufficient to determine a diagnosis. The color is due to the inhalation of dust which has become imbedded in the tissues. In this case the dust is composed of powdered chert which is an impure flinty rock, including the jaspers. In the stage of extreme fibrosis the sputum often becomes mucopurulent and is frequently blood streaked. Small *hemoptyses* are not uncommon. Of 433 cases of silicosis studied by Lanza (40), 33 per cent. of those in the first stage had hemorrhages; in the second stage, 10.5 per cent.; in the third stage, 20.5 per cent. of the uncomplicated cases and 30 per cent. of those with an added tuberculous infection. Night sweats are uncommon.

If there is an associated *bronchiectasis* located in the inferior portions of the lungs the sputum may be profuse and fetid in character. Dilatation of the bronchi at the apices, on the other hand, is not associated with excessive expectoration or fetor of the sputum as the drainage is good and stagnation of the bronchial secretions does not occur. In common with other individuals subject to chronic pulmonary lesions these patients are frequent sufferers from acute colds, and during such attacks the amount of sputum is markedly increased.

Shortness of breath on exertion or a more or less constant dyspnea sooner or later makes its appearance. In the case of true silicosis, dyspnea usually antedates the appearance of a cough and for a varying period of time may be the only symptom complained of. It is often more annoying than the cough and although in the milder cases it may be noticeable only on slight exertion, it is felt in the severer forms even when the patient is at rest. At times it has some resemblance to asthma, the breathing being wheezy in character. In such cases the inhalation of the dust seems to be the exciting factor. In a potter whom we had under observation the "asthmatic" symptoms entirely disappeared when he gave up the trade after being in it over forty years. The shortness of breath has been ascribed partly to the associated emphysema and partly to the replacement of pulmonary tissue by the fibrosis. A most important factor, in our opinion, is the functional capacity of the diaphragm. We found that in those cases in which both leaflets of the diaphragm were freely movable, shortness of breath was absent. This was so constantly the case that accordingly as the patient gave a history of being free from dyspnea or one indicating this symptom, we could predict the fluoroscopic findings in regard to the diaphragm. Those who have studied the effects of silica in the lungs of gold miners in South Africa state that shortness of breath on exertion is one of the earliest of the cardinal symptoms and is to be ascribed to the loss of pulmonary elasticity, as evidenced by diminished chest expansion (56).

As the disease advances a feeling of tightness and constriction of the chest is often present and in addition definite *pleuritic pain* may be complained of. In silicosis chest pain is often an early symptom and one that persists throughout the course of the disease although it may remit in the terminal stage. The location of the pain is variable but it is worth remembering that the pain or sense of tightness in the chest is often referred to the upper parts of the thorax—that is, in that portion where the early changes of pneumoconiosis first make their appearance.

The *general appearance* of the worker whose lungs show an early fibrosis is that of robust health. As the condition progresses, however, some impairment of the health may manifest itself. The individual reaction to the condition is, however, extremely variable. Some will show no appreciable deterioration in health in spite of marked fibroid changes, while others will begin to lose flesh, become anemic and even in uncomplicated cases, present a picture not unlike that of chronic tuberculosis. In the early stages the blood pressure is normal but as the process advances and the right heart dilates as the result of obstruction in the pulmonary circulation, the pressure is low.

Uncomplicated pneumoconiosis is often *afebrile,* or if fever is present it is very slight. The presence of any considerable amount of fever should arouse the suspicion that the condition is complicated by *tuberculosis.* The behavior of a tuberculous infection engrafted upon pneumoconiosis is subject to some difference of opinion. The teaching on this subject has, for many years, been to the effect that the clinical manifestations of the tuberculous disease were modified. This has certainly been my experience in the case of potters. Such patients do not look tuberculous; are afebrile, except in the terminal stage; and even then the temperature fluctuations are often not marked. South African observers, however, express the belief that with the occurrence of a tuberculous infection in those suffering from silicosis, the symptoms and signs are predominantly those of the former disease. Lanza, whose investigation was concerned with the same type of dust, namely silica, states that "even when tubercle bacilli are present in the sputum the lack of resemblance is plain and persists until the last few days' of life, when the patient being practically moribund, the resemblance to tuberculosis is more apparent."

It is to be borne in mind that the tuberculous infection, whether previously quiescent or due to a reinfection, is secondary in producing disability, though it may hasten death. While there are cases in which the tuberculous infection seems to exert but little influence on the general health of the patient, its tendency is to aggravate the symptoms and to cause a rapid decline in health. It is to be regarded in the majority of instances as a terminal infection.

Organic Dust

The inhalation of pure organic dust may temporarily cause some irritation of the upper respiratory tract and thus bring about coughing or sneezing or, if a foreign protein is inhaled, an asthmatic seizure may be induced. Other than these there are no symptoms as the type of dust is incapable, with rare exceptions, of causing structural changes in the lungs. The effects of organic dust have been fully discussed in the section on *etiology*.

PHYSICAL SIGNS

Inorganic Dust

In the great majority of cases nothing abnormal is to be detected in the so-called first or second stages of pneumoconiosis. This will be the case when the X-ray shows distinct evidences of changes, particularly in the second stage. Given the type of dust and the length of exposure one can hazard a shrewd guess as to the stage of the disease. When the disease enters the third stage, the physical signs are marked but not distinctive of the condition.

The physical findings in the third stage are as follows:

Inspection.—Expansion of the chest is usually deficient and may be more marked on one side than the other. There may be considerable retraction of one side of the chest and where this is present the heart will be drawn toward that side. Occasionally the chest is somewhat emphysematous in type. Clubbing of the fingers is commonly present and is indicative of an associated bronchiectasis.

Palpation.—This will aid in determining the degree of expansion on the two sides and the location of the apex beat of the heart.

Percussion.—If emphysema is present the note will be hyper-resonant. In the majority of instances, however, there are areas of dullness overlaying the dense fibrosis. The dullness is apt to be more marked in the mid-portion of the lungs and towards the apices. It may be greater on one side than the other. A tympanitic note may be elicited at the apex or near the angle of the scapula. When present it is an indication of bronchiectasis.

Auscultation.—The auscultatory signs are varied. The breath sounds may be diminished in intensity and broncho-vesicular in character. In many cases the breathing is rapid owing to involvement of the diaphragm. If the bronchi are dilated the breathing over the affected area is bronchial or cavernous; this may occur at the apex or near the angle of the scapula. In the latter area one can be almost certain that the signs are due to bronchiectasis while at the apex they may be due to this condition or to a cavity.

Râles of all descriptions may be heard all over both lungs. The condition may be mistaken for chronic bronchitis or owing to the wheezy character of the breathing and the presence of sibilant or sonorous rales, asthma may be suspected.

The voice sounds will vary—they may be suppressed in some areas and exaggerated in others; if the bronchi are dilated, both the spoken and whispered voice are readily transmitted at certain points, namely, the apex or about the angle of the scapula.

The heart shows nothing distinctive In the advanced stage evidences of dilatation of the right heart may be present.

Organic Dust

As no lesions are produced in the lungs by organic dust physical signs are lacking except in those instances where an asthmatic seizure is induced by the inhalation of a protein containing dust.

X-RAY EXAMINATION

The study of this condition by means of the roentgen rays is the greatest advance which has yet been made. In the past few years several excellent reports of this nature have been published. During the past two years Pancoast, Miller and I (57) have studied a large number of individuals who have been exposed to dusts of various sorts.

In regard to the effects of *organic dust* the subject can be dismissed with the statement that these individuals show no more marked changes than are encountered in those who have dwelt all their lives in large cities. When the evidence of pneumoconiosis is slightly more marked than normal in these cases, it is to be ascribed to the fact that there is a considerable amount of inorganic material mixed with the organic dust. This was notably so in a number of carpet makers we examined.

The roentgenologic picture in the case of those exposed to *inorganic* dust is, in the great majority of cases, characteristic, except perhaps in the very early stage. As a rule, the changes as seen in the roentgenogram correspond closely to the pathological processes.

The first stage is characterized by an increase in the hilus shadows and a thickening of the usually prominent trunk shadows, and an undue prominence of the finer linear markings. It is the rule that the increase in thickness of the bronchial trunk shadows is fairly uniform, which is the main dependence in distinguishing the case from one of peribronchial tuberculosis, but there are exceptions which make the roentgenologic diagnosis difficult or uncertain. The descending trunk shadows seem to be more marked on the right than the left but the interference offered by the heart shadow on the left side may hide a similar condition there. Abnormalities of the diaphragm excursion occur in all stages, even the first. In the first and second stages, however, there is no general rule. The position of the excursion during ordinary respiration between the limits of extreme inspiration and expiration is very variable. The most common finding, in our experience, was a restriction at the inner portion of the right leaflet during full inspiration and either a decided flattening or a concavity of the outer aspect.

The second stage is characterized by a more or less uniformly arranged mottling throughout the lung structure due to the deposition of dust in the lymph spaces, cells and fibrous tissue interspaces, with the addition of a certain amount of localized fibrosis. This stage comprises what has usually been regarded as the typical case of pneumoconiosis. Its onset seems to depend largely upon the character of the dust inhaled. It occurs early in those exposed to silica, comparatively early in coal miners, certain metal grinders and somewhat later in potters and asbestos workers. The distribution of the mottling was found by us to appear invariably first on the right side on a level with the hilus shadow. It certainly becomes quite perceptible on the right side before it appears on the left side and for some time after it does appear on the left side, it is noticeably more marked on the left. In the advanced stage the two sides seem to be about equally involved. The distribution is more or less symmetrical, but naturally not uniform throughout the lung. From the starting point it gradually spreads to the bases and apices, but is never so marked at the extreme apex or base as around the mid-portion of the lung. The appearance of the mottling depends more or less upon the character of the dust. In those exposed to silica the spots are very dense and sharply circumscribed and can be seen when very small. In the case of the less irritating forms of dust the spots are not so sharply defined. The roentgenologic diagnosis in this stage is not difficult. It may be difficult, however, to detect an early tuberculous lesion engrafted upon a well advanced case of pneumoconiosis in the second stage.

The *third stage* is characterized by the appearance of diffuse fibrosis and all that the term implies. While there is no sharp dividing line between the second and third stages, it would appear in some instances that the mottled appearance in the second stage becomes more and more conglomerate and finally passes over into the appearance of dense fibrosis. In other instances a general haze seems to spread over a certain portion of the lung. The greatest density is in the sub-apical regions, although this is not the area of most intense mottling in the second stage. Dense fibrous bands can be seen extending in various directions, and frequently to the diaphragm, causing marked retraction. In this stage the mottling has become extremely coarse and sometimes is to be no longer recognized as such. The heart and blood vessels are frequently dragged out of place and bronchiectatic cavities are quite common.

It is not always easy to differentiate between the fibrosis resulting from tuberculosis and pneumoconiosis and were it not for repeated negative sputum examinations, sometimes extending over a number of years, it would not be easy to say that tuberculosis was not present.

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RESPIRATORY SYMPTOMS DUE TO LATENT SYPHILIS

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DISPENSARIES and hospitals dealing with the care of tuberculous individuals receive during the course of a year a very considerable number of patients who are either not tuberculous or in whom a diagnosis of tuberculosis is open to doubt. Frequently the patient is referred to the dispensary or sanatorium by a physician; again the patient, because of more or less marked respiratory symptoms, seeks medical advice on his own initiative. The problem in all instances, especially as regards the dispensary, is to establish, in so far as it is possible, a definite diagnosis. For some years the criticism has been made of dispensaries and to some extent of sanatoria, that they carry on their lists many patients in whom the diagnosis of tuberculosis is questionable. It is desirable that the diagnosis should be open to as little doubt as possible, not only on account of the patient's peace of mind, but also for economic reasons. It is quite apparent that individuals who do not suffer from tuberculosis or those who harbor old, arrested lesions should not be subjected to sanatorium treatment, as they not only cause the State needless expense, but in addition confuse our notions of both the frequency and the curability of tuberculosis.

If the dispensary is to carry out properly the function of a clearing house, each case must be carefully studied. The one factor which places the diagnosis of tuberculosis beyond question is the presence of tubercle bacilli in the sputum. Such a finding establishes the diagnosis beyond a question of a doubt. Unfortunately this group of cases is made up for the most part of the far advanced and the moderately advanced type of the disease, in which the symptoms, physical signs, and course of the illness make the etiology

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reasonably certain. The real trouble is in dealing with that group in which the symptoms range from those suspiciously tuberculous in origin to those almost certainly so, but in which the physical signs are inconclusive and tubercle bacilli are absent. The number of patients in this group who finally will be designated as tuberculous will depend largely on the policy of the particular institution. In one a liberal attitude will be taken and the number of positive diagnoses will be correspondingly large; in another a spirit of skepticism prevails with a correspondingly small number of positive diagnoses.

In studying patients who are not definitely tuberculous, many can readily be shown to be suffering from some well-recognized lesion of the lungs, pleura, or heart. But after we have eliminated those in whom the respiratory symptoms are explainable by reason of the history, the location of the lesions or the bacteriological findings, we are still confronted with a considerable number in whom it is often difficult to give a definite opinion. In this group the symptoms are usually strongly suggestive of pulmonary tuberculosis. The physical signs may be typical of those encountered in tuberculosis, but often abnormal physical findings are absent or very slight in proportion to the severity of the symptoms. The discovery of the etiological factor is the all important thing in this group. If the examination of the sputum repeatedly fails to show the presence of tubercle bacilli, careful search should be made for one of the mycotic organisms. If the latter can be ruled out, a chronic inflammatory condition probably exists. The etiology of these conditions is often difficult to establish. Fibrous tissue can arise from such a variety of causes that it is not easy to determine in its final stage what the initial process was. Among the possibilities is syphilis.

Even before the discovery of the *Spirochæta pallida*, and later the introduction of the Wassermann test, it was universally recognized that syphilis was one of the most protean of all diseases. It was generally admitted that it might exist in a latent form for years and from time to time manifest itself, sometimes in the guise of other diseases, in other instances by obscure symptom complexes. To such an extent was this true that it has been traditional for years that in all obscure conditions syphilis is always to be thought of as the possible etiological factor. Medical literature abounds in

instances in which the acting on such a suspicion has resulted in the most brilliant therapeutic results.

It is hardly necessary to recall the conditions which have always been regarded as being probably syphilitic in origin, namely, general paralysis of the insane, tabes dorsalis, thoracic aneurysm, etc. We now possess the knowledge that makes it possible to remove these conditions from the class of probable manifestations of syphilis to that which is certainly luetic in origin. In other instances, syphilis is believed to be the exciting factor, although the final result differs in no particular from that produced by other etiological factors.

So rapidly has our knowledge of syphilis been extended since Schaudinn's momentous discovery and Wassermann's introduction of the complement fixation test, that one is probably safe in saying that there is no tissue of the body which is immune to its ravages; and although we lack the specific proof that this is true in every instance, enough has been done to make it highly probable that ultimately the final demonstration will be supplied.

Among the viscera which are regarded as especially resistant to syphilis are the lungs. Prior to the discovery of the tubercle bacillus, pulmonary syphilis was regarded as being relatively frequent, and the older literature contains numerous references to the subject. After the discovery of the tubercle bacillus and the clarifying of our views as to the lesions produced by this organism, it became apparent that many of the cases reported as being examples of syphilis of the lungs were in reality tuberculous in nature. There then followed a period in which the diagnosis of pulmonary syphilis was rarely made, and indeed up to the present time such a diagnosis is regarded with a certain degree of skepticism. This attitude has been brought about almost entirely by the pathologist, who demands the etiological or anatomical proof. Fortunately or unfortunately, as the case may be, the majority of the clinical observations have resulted in cures, and therefore, aside from the Wassermann reaction and the therapeutic test, other proof is, as a rule, wanting.

Several years ago our attention at the Phipps Institute was directed to syphilis as the possible cause of respiratory symptoms in patients in whom it was impossible to establish a definite diagnosis

of tuberculosis. These observations were recorded in a paper by Lewis and myself.[1] It is significant that of the six cases recorded by Lewis and myself three had spent some months each at a tuberculosis sanatorium, and of the cases reported below two were subjected to this treatment.

Our belief that syphilis of a latent type might be the cause of persistent respiratory symptoms arose from the fact that patients were occasionally encountered in whom the symptoms and physical signs were strongly suggestive of tuberculosis, but in whom neither the tubercle bacillus nor other less familiar organisms could be demonstrated. Furthermore, the Wassermann reaction was strongly positive, and in addition some of them had well-marked syphilitic stigmata. Since that time we have continued these observations: (1) by a more extended application of the Wassermann test and (2) by a routine examination of all patients for possible syphilitic stigmata.

As a result of our observations during the past two or three years we have encountered the following examples of what we believe to represent a latent type of syphilis which manifests itself chiefly by respiratory symptoms.

Case I. (Phipps Institute No. 15,263.) Male, white, age fifty-seven. He gave a history of having had a chancre in his youth. Eight years prior to being seen at the dispensary, he had an attack of pleurisy at the right base (probably a perihepatitis). He gave a history of having had a cough with whitish expectoration for one year. During this time his weight had fallen from 198½ to 160½, and for the past eight months he had been unable to work. He had an irregular type of fever ranging from normal to 100° F.

Physical examination showed some flattening beneath the right clavicle with impairment of the percussion note both anteriorly and posteriorly over the right apex. The breath sounds were broncho-vesicular in character over this area and posteriorly fine submucous râles were heard. An *x*-ray examination of the chest showed the presence of some connective tissue at the base of the right lung. This extended upwards along the bronchial trunks. In addition there was a diffuse shadow over the right upper lobe which obscured the lung details. The aorta was tortuous.

Because of repeated negative sputum examinations and a plus 4 Wassermann, the patient was placed on antisyphilitic treatment. In a

[1] *Am. J. M. Sc.*, Aug., 1915.

few weeks he began to gain in weight. The respiratory symptoms gradually disappeared, as did also the râles at the right apex. In the course of two months he resumed his work. When last seen he was free from symptoms and his weight was 195.

Case II. (Phipps Institute No. 16,817.) Female, white, age twenty-four. Married, two miscarriages—one child died of hereditary syphilis. She gave a history of having had pain in both sides of the chest, cough, and expectoration for two and a half years. On several occasions her sputum was blood-streaked. For the past two years she had some dyspnea and for two months hoarseness. Her weight had fallen from 116 to 76 pounds.

Physical examination showed the presence of numerous asthmatic râles throughout both lungs. She was sent to a tuberculosis sanatorium by a social agency and remained for several months; during this time she regained some weight. The diagnosis at this institution was "advanced tuberculosis" in spite of the fact that her sputum was negative for tubercle bacilli. On her return to the Phipps Institute her Wassermann was found to be plus 4. This fact and the history of two miscarriages led to the giving of antisyphilitic treatment. As a result of a course of treatment with salvarsan her pulmonary signs disappeared entirely, she gained in weight, and at the present time presents every appearance of being well.

Case III. (Private patient.) Female, white, married, age twenty-eight. This patient requested an opinion as to whether she had tuberculosis. She stated that she had suffered from respiratory symptoms off and on for eight years and that on two occasions, for periods of four months each, she had been sent to a tuberculosis sanatorium. Her trouble had started eight years ago with a severe cough and expectoration which lasted for eight months. Two years ago she had what she described as "three touches of pneumonia." During this entire time she had never been entirely free from cough. Her expectoration was often blood-tinged and at times she had some fever; at present she tires easily. For the past four years she had been troubled with nasal catarrh and slight deafness.

Physical examination. The patient was a well-nourished woman. Aside from a suspicious flattening of the bridge of the nose nothing abnormal was found. The lungs were remarkably free from any abnormality in spite of the long history of respiratory trouble. Fluoroscopic examination of the chest showed nothing abnormal. The fact that she had left her husband because of his dissipated habits, and the history of probable gonorrheal salpingitis, suggested the possibility of a luetic infection also. Additional factors were the deafness, nasal catarrh, and the flattening of

the bridge of the nose. The Wassermann reaction was plus 4, and repeated examinations of the sputum have failed to show tubercle bacilli.

Case IV. (Phipps Institute No. 15,652.) Female, white, married, age thirty-nine. One still-born child. Had suffered with dyspnea for two years. For four months had had hoarseness, cough, and yellow expectoration. Since the onset of her illness she had lost 22 pounds in weight. During the time she was under observation she had slight fever of an irregular type.

Physical examination showed some impairment of the percussion note, broncho-vesicular breathing and fine râles at the right apex. The sputum was negative for tubercle bacilli, and the Wassermann reaction plus 4. Under antisyphilitic treatment (mercury and iodide) the symptoms disappeared, the physical signs cleared up and she gained 21 pounds in weight.

Case V. (Phipps Institute No. 16,365.) Male, negro, married, age thirty-five. When first seen he gave a history of having had a cough and expectoration and pain below the left scapula for one year. Had also had considerable dyspnea for eight months. During this time he had lost 22 pounds in weight. The sputum did not contain tubercle bacilli and the Wassermann reaction was plus 4.

Physical examination showed the presence of subcrepitant râles at the bases of both lungs. Under the use of antisyphilitic treatment (mercury and iodide and later salvarsan) he regained the 22 pounds loss in weight and showed marked improvement in both the symptoms and physical signs.

In submitting these cases as examples of pulmonary syphilis, I clearly realize that the absolute proof demanded by the pathologist is lacking. On the other hand, these patients responded as readily to antisyphilitic treatment as do those suffering from luetic lesions in other portions of the body—the etiology of which is beyond cavil.

In the series of cases here presented as well as in those detailed in our previous paper, it is evident that we have to deal with instances of disease marked predominantly by respiratory symptoms. The constitutional effects are by no means trivial, in fact have been profound in several instances. The physical signs and the results of *x*-ray examination have frequently shown the existence of diffuse or localized lesions of some degree of severity. Serum examination has revealed a positive Wassermann reaction. The cases have been much improved or even apparently cured by antisyphilitic treatment.

The results of the Wassermann reaction and the response to treatment render it probable that the cases are syphilitic in origin. It is, of course, true that the examination of the chest has revealed no lesions of this type, or of the severity ordinarily recognized at the post-mortem table as syphilis of the lung. It seems not improbable that lesions of pulmonary syphilis other than the classical may exist. In view of the frequency with which the mucous membranes of the mouth, naso-pharynx, and larynx become ulcerated in syphilis, it is certainly not improbable that a syphilitic bronchitis may at times exist. Nor is it unlikely that patches of syphilitic pneumonia may develop either independently or as extensions from a preceding bronchial condition. If these assumptions be admitted, the syphilitic nature of these cases, and as a corollary the existence of syphilitic lesions of the lung, other than those described by pathologists, is clear.

If, on the contrary, it is held that the descriptions already furnished of syphilis of the lung are complete, then another explanation for at least a part of the cases presented is in order. In view of the positive Wassermann reaction and the response to treatment, it would be logical to assume that we have to deal with some form of spirochæte infection other than syphilis. French and Italian observers recognize a form of spirochætal bronchitis, but it is not known to exist in America. It must be acknowledged that such an explanation of these cases is possible. In its favor perhaps may be the fact that certain of these cases have yielded to treatment with ease. Syphilis of the mucous membranes is also easy to cure. It is, however, as a rule, very difficult to secure permanently negative Wassermann reactions in late syphilis, and this seems to have been the result in certain of these cases, although the period of observation is still too short to enable one to speak with finality on this point.

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OBSERVATIONS ON THE WASSERMANN REACTION.

A Comparison of the New System of Noguchi with That Using Cholesterolized Antigen According to McIntosh and Fildes.

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(Received for publication, January 23, 1919.)

Among the many modifications of the Wassermann reaction, that of Noguchi,[1] introduced a number of years ago, in which use is made of the acetone-insoluble lipoids extracted from certain tissues and the anti-human hemolytic system, is doubtless the most promising from a theoretical standpoint. In practice we had found it a troublesome system to apply particularly because the collection of the human cells for the immunization of rabbits and carrying out the tests is laborious and time-consuming, and also because the production of the anti-human amboceptor in the rabbit is less satisfactory than that of anti-sheep amboceptor. We had come to the conclusion that if a certain allowance was made for reactive anti-sheep amboceptor, as can be done by an intermediate incubation period of 15 to 20 minutes after adding the sheep cells, but before adding the anti-sheep amboceptor, the results did not differ materially from the human hemolytic system. For a long time we used the Noguchi antigen with satisfaction.

McIntosh and Fildes[2] presented an application of a principle introduced by Sachs (the addition of cholesterol to alcoholic tissue extracts), and Richardson[3] compared the reactions with this "choles-

[1] Noguchi, H., Serum diagnosis of syphilis, Philadelphia, 1910.

[2] McIntosh, J., and Fildes, P., An investigation of the value of certain antigens for use in the Wassermann reaction, in particular of Sach's new antigen, *Z. Chemotherap., Orig.*, 1912–13, i, 79.

[3] Unpublished observations at the Pennsylvania Hospital.

terolized antigen" with those obtained with the Noguchi antigen with the anti-sheep hemolytic system. He studied about 2,000 reactions, and, like other investigators, found that the cholesterolized antigen gave the higher percentage of positive reactions, but that in most cases this was justified by the facts. Eight cases were found in which there was no evidence of syphilis other than the positive reaction, but there was no evidence to the contrary and it was considered that the result was on the whole satisfactory. This antigen is the easiest to obtain in quantity and is of relatively constant quality as compared with others. It was therefore adopted and has been used continuously for a number of years in these laboratories. More recently the carrying out of the reactions has passed into other hands, and we have had some reason to question the accuracy of the opinion previously held as to the safety of the cholesterolized antigen from the diagnostic point of view.

In the meantime, opinion elsewhere seems to be divided. Some competent observers have found the cholesterolized preparation satisfactory. In the hands of others it seems to be too sensitive; that is, it gives rise to false positives.

Recently Noguchi[4,5] has proposed the use of the native human complement in the reaction with his acetone-insoluble lipoids as antigen. He states that with the quantities he specifies satisfactory results can be obtained, fully comparable with those derived from the use of his older system. This system makes unnecessary the continued collection of guinea pig serum, and this may be expected to compensate for the trouble in regard to human red cells. It is, of course, of importance at times to be able to carry out the method when guinea pig serum may not be available.

We have attempted, therefore, to review the question of the Wassermann reaction as practically applied with the purposes of (1) reconsidering the suitability of the cholesterolized antigen, and (2) examining the merits of the newer Noguchi system.

[4] Noguchi, H., A method of facilitating the serum diagnosis of syphilis under war conditions, *J. Am. Med. Assn.*, 1918, lxx, 1157.

[5] Noguchi, H., A homohemolytic system for the serum diagnosis of syphilis, *J. Exp. Med.*, 1918, xxviii, 43.

RESULTS.

It has been assumed on the basis of the author's report that the two systems of Noguchi would have equal value and that comparison of one of them with the results by cholesterolized antigen should

Noguchi antigen \ Cholesterolized antigen	++++	+++	++	+	0
++++	48	4	5	4	4
+++	9	6	2	0	2
++	11	5	6	5	6
+	8	1	4	6	2
0	11	2	21	27	188

TEXT-FIG. 1. The figures in the chart indicate the number of sera giving deviations as indicated with both the cholesterolized antigen and according to Noguchi's homohemolytic system. The total comprises 387 different sera.

establish the place of the latter. We have therefore done our reactions comparing the newer Noguchi system with the system which makes use of cholesterolized antigen and the anti-sheep hemolytic reagents. The general results are displayed in Text-fig. 1.

It is apparent that in a large majority of the cases the two methods of work have an equal value (central diagonal space) or one essentially equal (adjacent diagonal spaces). It is also clear that the numbers toward the lower left corner (cholesterol reaction positive, Noguchi reaction negative) considerably outnumber those toward the upper right (cholesterol reaction negative, Noguchi reaction positive). In other words, the cholesterolized antigen is considerably more reactive.

Which method develops the facts most nearly in accord with the truth as to the existence of syphilis in the particular cases? Of the ten cases in which the Noguchi system gave a positive and the other a negative or weak reaction, eight were unquestionably syphilitic. One of the others was possibly syphilitic. In the tenth case, that of an apparently healthy young man with a fractured jaw, no decisive evidence could be obtained. In all these cases except one, who was an undoubted syphilitic, doubling the amount of serum used (making 0.2 cc.) in the reaction with the cholesterolized antigen perceptibly increased the intensity and in most instances rendered it entirely positive.

Material.

Before taking up the question of whether a positive reaction with the cholesterolized antigen means syphilis, even though the Noguchi reaction be weak or absent, it is perhaps best to consider the material which we have had for study. The majority of our reactions were carried out on known cases of syphilis, who were under treatment. In most of these the evidence of disease was clear apart from the Wassermann reaction. Most of the cases which showed a positive cholesterol and negative Noguchi reaction come in this group. As controls we examined the blood of twenty-nine persons in good health who were sufficiently known to us to make it appear improbable that they were suffering from syphilis. One of these gave +++ reaction with cholesterolized antigen and on the same occasion gave a ++ Noguchi reaction. On another occasion the same person gave a ++ cholesterol and a negative Noguchi. Two others in the group gave a ++ cholesterol reaction and a negative Noguchi. Further, the blood of 109 patients at one time available in the hos-

pital was examined without selection. Whether by chance or not these results, which will be considered in detail later, do not bear on the present point as the two reactions were practically alike in all instances.

Of the cases in which the cholesterol reaction was positive (++++ or +++), the Noguchi reaction being at the same time weak or negative, five could not be satisfactorily determined although there is no reason to believe that the reaction is in error. The remainder were definitely syphilitic and there is every reason to believe that the reaction with cholesterolized antigen is a better expression of their condition than that done by the Noguchi method.

There are twenty-one reactions showing a ++ cholesterol with a negative Noguchi reaction. In this series these reactions are for the most part the evidence of a fading out of the activity of the serum in the course of specific treatment. In view of the three reactions of similar intensity among twenty-nine probably normal individuals such degrees of activity cannot, of course, be held to be of any decisive value from a diagnostic view-point. Whether the six instances in which the Noguchi reaction was ++ and the cholesterol reaction negative are similarly lacking in diagnostic significance may be open to question, but we are inclined to the belief that they are, except, as may sometimes happen, when doubling the amount of test serum leads to a stronger reaction with cholesterol.

Interpretation of Results.

In view of the results in the unselected series of patients in the hospital, it appears to be useless to discuss the question of just which intensity of reaction, with either antigen or both, justified a diagnosis of syphilis. Among these 109 persons there were several cases in whom the diagnosis of syphilis was presumptive on other grounds. These gave clear-cut reactions with both systems. There were two patients who gave ++++ Noguchi reactions with weak cholesterol reactions. The status of these cases remains in doubt. In addition, the cases shown in Table I gave more or less reaction.

These cases comprise about half the febrile cases in the hospital at the time. The others, rheumatic fever, endocarditis, and lobar pneumonia, as well as about 50 cases in the surgical wards, gave

negative reactions. It is evident, therefore, that the Wassermann reaction must be used with some caution and that it must always be valued in conjunction with a presumptive diagnosis based on other grounds. With these facts in mind it may be fairly stated that from the point of view of establishing a diagnosis the two forms of reaction have approximately equal value. The cholesterol reaction is somewhat more sensitive and the weaker grades are to be viewed with a little less confidence perhaps than similar weak reactions with the Noguchi system. Whenever possible there would

TABLE I.

Case No.	Diagnosis.	Cholesterol reaction.	Noguchi reaction.
13	Typhoid fever	+++	++++
16	" "	++	0
18	" "	++++	+++
20	Heat stroke	+	0
24	Typhoid fever	++++	++
25	" "	++++	++
26	Heat stroke	++++	++++
28	Typhoid fever	+	0
29	Heat stroke	+	0
30	Lobar pneumonia	+++	+
45	Gastroenteritis	0	++
54	Asthma	0	++
57	Tuberculosis; peritonitis	++	0
58	Acute enteritis	0	++

appear to be a real advantage in viewing the two systems side by side, holding for particularly careful scrutiny cases in which the results do not check.

Fully as important as its application to diagnosis is the use of the Wassermann reaction as a control for treatment. Here any difference that may exist in sensitivity is in favor of the continued use of the cholesterolized antigen. It may also be profitable to use the two systems side by side. One purpose of this would again be that of having a precautionary check. There is imperfect evidence in our hands, however, that under treatment the two systems may vary in some degree independently of one another, and it is possible that useful information may be obtained by following out this suggestion.

Up to this point we have spoken of these two types of reaction as though the results with either were always unmistakable and arrived at without difficulty. This is by no means the case. Exception has frequently been taken to the use of cholesterolized antigen because of irregularities which develop with successive reactions with the same samples of serum. In order to make the reaction safe it seems to us necessary to use a slight excess over the amount of complement usually advised for Wassermann work. Our custom is to use $2\frac{1}{2}$ units of both complement and amboceptor. The final antigen dilution should be used within a few minutes after it is made and should be made in accordance with McIntosh and Fildes' directions; that is, the mixture with salt solution should be rapidly accomplished. We put the salt solution (24 cc.) in an Erlenmeyer flask of 50 cc. capacity, float the alcoholic solution very carefully on the surface, and then mix the two with one quick vigorous shake. The titration of reagents is carried out completely each time on the basis of $\frac{1}{2}$ hour incubation in the water bath and the incubation after the addition of the hemolytic system is likewise $\frac{1}{2}$ hour.

Neither is the Noguchi system in its present form free from difficulty. It should be noted that in the two publications on the subject Noguchi has recommended the use of two different quantities of human serum. He first suggested 0.1 cc. as the proper quantity, later changing this to 0.2 cc. in his final paper. Neither recommendation appears to us to be adequate. As a matter of actual observation there are great differences in the susceptibility of various samples of human red corpuscles to hemolysis by human complement and rabbit anti-human amboceptor. These differences are quantitatively such that a given serum may present insufficient complement for the reaction or may have more than four units. From 70 consecutive tests we found that with susceptible corpuscles every fresh human serum has complement sufficient for the test. Certain sera with these corpuscles may contain as much as eight units of complement. With resistant corpuscles no serum may have more than two units and one in ten may show no complement whatever. An intermediate condition is more common and was evidently encountered by Noguchi. If exact work is to be done account must be taken of these facts.

We have found it best to conduct each test with three quantities of serum, 0.2, 0.1, and 0.05 cc., each quantity having its antigen and control tubes. The result is then scarcely ever in doubt. It would doubtless be still better to standardize the reaction to a certain extent by selecting a single suitable person, preferably one with susceptible corpuscles, as a source of the red cells.[6] If this were done it would probably be safe to rely on two of the above quantities of serum, either the greater or the lesser pair as the susceptibility of the cells indicated.

Another objection to the system which at first sight seems important is negligible in practice. It is obviously impossible to control the anticomplementary value of the antigen for each separate complement where the complement is furnished by the test serum. The antigen which we have been using has had an apparent anticomplementary value of about ++ on the unit value of complement and this can be allowed throughout the tests whenever deviation occurs. For each lot of antigen this would necessarily be determined by comparative observation on a number of negative sera. Noguchi speaks of his antigen's being entirely without anticomplementary value in the quantity recommended. In this particular our application of the method can doubtless be somewhat improved upon.

SUMMARY.

The Wassermann reaction carried out according to the method of McIntosh and Fildes, with cholesterolized antigen and with certain allowances for the presence of native anti-sheep amboceptor, leads to about the same result as when it is done according to the recent proposal of Noguchi, with the native human complement and acetone-insoluble lipoids as antigen. The differences are such as to suggest that from the point of view of diagnosis the Noguchi method is the more conservative but that there is definite advan-

[6] Observations which have been begun but are as yet unfinished indicate that the source of variation in the resistance of the corpuscles may be sought rather in the way the cells are kept or their age outside the body than in any true variation from person to person. The outcome of this study in no way influences the practical significance of the considerations put forward above.

tage in using two methods as distinct in origin of materials as these, partly for the purpose of control and partly in the hope of acquiring new information of importance. As a measure of control of treatment the cholesterol antigen appears to us to be the more valuable. The Wassermann reaction alone, by whatever method it may be done, can only be used in the diagnosis of syphilis in conjunction with presumption based on other grounds. That it fails to appear in a considerable percentage of syphilitics is well known. That the reaction is positive in other conditions is not so generally recognized. Fresh instances of this in certain febrile cases are here recorded.

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ABSORPTION SPECTRA OF ACID HEMATIN, OXYHEMOGLOBIN, AND CARBON MONOXIDE HEMOGLOBIN. A NEW HEMOGLOBINOMETER.

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(Received for publication, January 24, 1919.)

This paper contains spectrophotometric data on two hemoglobin derivatives. The transmissions of solutions of oxyhemoglobin, acid hematin, and carbon monoxide hemoglobin for light in the visible and ultra-violet portions of the spectrum are given. The data have a certain abstract interest. They serve to correlate properly spectrophotometric values with oxygen capacity. The immediate purpose in securing them was that they might serve as a basis for work on colorimetric hemometers, a problem which is discussed at the end of this paper. The optical properties of a new hemoglobinometer are described.

HISTORICAL.

The visible bands of oxyhemoglobin first described by Hoppe-Seyler (1) have received considerable attention, more particularly as regards their position. Soret (2) was the first to recognize the great ultra-violet band of oxyhemoglobin, a band which he observed with a fluorescing eyepiece. Later Gamgee (3) using a quartz spectrograph and the sun as a source, made a more extensive investigation of the ultra-violet absorption spectra. He showed that the great ultra-violet band was common to oxyhemoglobin, reduced hemoglobin, CO- and NO-hemoglobin, hemochromogen, hematin hydrochloride, methemoglobin, and hematoporphyrin. Gamgee did not find such a band in the spectra of bilirubin, hydrobilirubin, or urobilin. A paper by Rost, Franz, and Heise (4) contains excellent plates of the spectra of many of the hemoglobin derivatives, together with an extensive summary of earlier work. Lewin, Miethe, and Stenger (5) have also published extensive qualitative spectrographic data of this sort.

Rollett (6) gives a picture, only roughly correct, showing the change in width of the absorption bands of oxyhemoglobin with dilution. Vier-

ordt (7) was the first to study the quantitative absorption of these compounds throughout the visible spectrum. His tables and curves were made on a very early type of spectrophotometer having large instrumental errors. Cherbuliez (8), in 1890, published certain spectrophotometric data on the hemoglobins which he had made with an improved instrument. His absorption curves given for the more central portions of the visible spectrum are more nearly correct. The α-band of oxyhemoglobin is given as shallower than the β-band, an error difficult to avoid because of the disturbing effect of the very high transmission to the red side of the α-band.

Aside from these two determinations of absorption curves there have been many determinations of certain absorption constants and relations, in part undertaken with the view of fixing a spectrophotometric method for the quantitative determination of oxyhemoglobin and other hemoglobins.

If T is the fraction of light of a given wave-length transmitted by a substance, then the equation $T = 10^{-e}$ defines a number e known as an extinction coefficient. The extinction coefficent is the cologarithm of the transmission. It was first shown by Beer (9) that for a solution a simple absorption relation exists between the concentration, c, the thickness, t, and the extinction coefficient, e; namely, $\frac{ct}{e} = \text{constant}$. This equation holds under a wide range of conditions. For oxyhemoglobin, carbon monoxide hemoglobin, and acid hematin it would seem at least to hold within the range of dilution here used (whole blood 1:100 to 1:2,000). Butterfield (10) has shown that the relation holds in the case of oxyhemoglobin for a range of dilution of whole blood 1:1 to 1:160. Reid (11) has shown that oxyhemoglobin forms a true solution.

While e is understood to be the extinction coefficient for a single wave-length, practically it is the mean e for a sufficiently small spectral interval, the interval given by the exit slit of the spectrophotometer. The value of the constant of the equation being determined at such an interval for a known concentration, c, this value furnishes a basis for the calculation of any c by the instrumental determination of the e. By properly choosing the spectral interval and using concentrations giving extinction coefficients within a certain optimal range, the determination may be made to within 1 per cent. With uniformity in slit widths such determinations are absolute, variations between different in-

struments being only within observational errors of the individual instrument.

With the thickness of solution equal to 1 cm. it has become customary to designate the constants by the letter A. The ratio of two such constants determined for two separate spectral intervals is a ratio independent of the concentration and a characteristic of the substance.

$$\frac{A'}{A} = \frac{c'/e'}{c/e} = \frac{e}{e'}$$

The principal determination of the values of these constants A_0 and A_0' for oxyhemoglobin, are as follows:

Hüfner (12, 13)

$A_0 = 2.070$ (5540 to 5650 Ångström units)[1]

$A_0' = 1.312$ (5315 " 5425 " ")

$\frac{A_0}{A_0'} = 1.578.$

[1] The Ångström unit is one ten-millionth of a mm. or one ten-thousandth μ. The Fraunhofer lines often referred to as reference lines have the wave-lengths in Ångström units given below. The values due to Rowland are corrected on the basis of the accepted values for the primary standard cadmium line and the secondary standard iron arc lines of Fabry-Buisson (see Fowle, F. E., *Smithsonian Miscellaneous Coll., Publication 2269*, 1918, lxiii, No. 6):

	Å. u.		Å. u.		Å. u.		Å. u.		Å. u.		Å. u.
B	6867.2	E_2	5269.55	F	4861.35	L	3820.44	Q	3286.76	T	3020.65
C	6562.8	b_1	5183.62	G	4307.92 4307.75	M	3727.64	R	3181.26 3179.33	t	2994.42
D_1	5895.95	b_2	5172.69	h	4101.85	N	3581.19	S_1	3100.67	U	2947.89
								S_2	3100.31 3099.93		
D_2	5889.98	b_3	5169.05 5168.90	H	3968.48	O	3441.00 3440.61				
E_1	5270.39 5270.27	b_4	5167.51 5167.33	K	3933.68	P	3361.18	s	3047.61		

Cherbuliez (8)

A_0 = 2.038 (5530 to 5580 Ångström units)
A_0 = 1.326 (5360 " 5410 " ")
$\frac{A_0}{A_0'}$ = 1.537

De Saint Martin (14) (polarization spectrophotometer)

A_0 = 2.153 (5572 to 5683 Ångström units)
A_0' = 1.330 (5380 " 5490 " ")
$\frac{A_0}{A_0'}$ = 1.621

Bardachzi (15) (polarization spectrophotometer)

A_0 = 2.094 (5540 to 5650 Ångström units)
A_0' = 1.334 (5315 " 5425 " ")
$\frac{A_0}{A_0'}$ = 1.56

Butterfield (16) (polarization spectrophotometer)

A_0 = 1.87 (5561 to 5646 Ångström units)
A_0' = 1.18 (5335 " 5420 " ")
$\frac{A_0}{A_0'}$ = 1.58

Butterfield (17)

α_1 = 18.42 (green mercury line, 5459 Ångström units)
α_2 = 21.00 (yellow " lines, 5770 and 5790 Ångström units)
(α represents the Napierian cologarithm of the transmission of a 1 per cent solution.)

Butterfield's figures for A differ from those of other reliable observers by approximately 11 per cent. In determining the transmissions by oxyhemoglobin of the green mercury line or the two very adjacent and equal yellow mercury lines many of the technical difficulties connected with accurate spectrophotometric measurements disappear. Care no longer needs to be exercised in making wave-length measurements; there is much more latitude in the choice of slit width relations and various reflection errors are removed.

The α_1 and α_2 given by Butterfield might be transformed to correspond to the notation otherwise used:

A_0^{546} = 1.25
$A_0^{577,\,579}$ = 1.096

EXPERIMENTAL.

Apparatus.

The apparatus used was a Hilger sector photometer and quartz spectrograph, size C, giving a spectrum 18 cm. long, extending from 2100 to 7000 Ångström units. The light from a single source passed by means of appropriate quartz prisms along two separate and symmetrical paths, one above the other, in each of which was placed a so called rotating sector consisting of a circular disk with two symmetrical open sectors. The openings of the lower rotating sector were fixed in size and each was a quadrant. The openings in the other could be varied from 90–0°. To the sector photometer was bolted the absorption cell so that it could be easily demounted for filling and returned to exact alignment. The double absorption cell was made from a single piece of plate glass by drilling it with two holes slightly larger than the two beams of light and exactly centered on them. Through the edge of the glass plate entrance holes were drilled into the first ones. Windows of plane clear quartz were then fastened on each face of the glass plate with DeKhotinsky cement, thus making two cells each 1 cm. thick.

This construction gave a rigid alignment of the cells in symmetrical position with respect to the light paths. In the upper cell was placed distilled water and in the lower the absorption fluid. The absorption of the cell itself was thus corrected for at first hand. Opposite the lower cell was the fixed opening sector, and opposite the upper cell the variable sector.

The light coming along the two paths fell in juxtaposition on the collimator slit of the spectrograph and passed parallel in two beams to be dispersed into two spectra, one directly above the other, and so photographed on the plate. By varying the opening of the one sector the exposure of this comparison beam was cut down one step at a time. Twenty-four such simultaneous pairs of spectra could be taken on one plate. The wave-length at which a pair of spectra matched in density was the wave-length having an extinction coefficient corresponding to that sector opening. In a paper by Howe (18), and in one by myself (19), it has been quite conclusively shown that the extinction co-

efficient is the logarithm of the ratio of the fixed to the variable opening.

The plates used were the Wratten and Wainwright panchromatic of London, and of Eastman manufacture. They were given tank development according to the formulas accompanying them. The iron spark, or for the mid-visible spectrum sometimes the D lines of the sodium flame were always photographed on the plate as a comparison scale and used in connection with a wave-length scale furnished for the instrument by Hilger. The scale as checked against the spectra of several metals had errors less than the width of the smallest interval in which the two spectra could be compared.

The light source for the ultra-violet determinations was a condensed iron spark, and for the visible, a Nernst lamp with the filament vertical. At the beginning and end of each plate exposures were made with both cells filled with water in order to show that the two dispersed beams were of equal intensity, or to determine the relative sector openings required to give such equality. After the instrument was in adjustment a balance, with equal sector openings, could be obtained correct to within an extinction coefficient of $\frac{1}{100}$. To compensate for this error the sector settings required for balanced beams were included on each plate and the extinction coefficients corrected by the addition of this balance constant in each case. The plates often balanced to within a fraction of $\frac{1}{100}$. For the ultra-violet the balance was not determinable with as much precision, the smallest observable correction being about $\frac{1}{100}$. In making exposures it was possible for one sector to present its opening once oftener than the other sector. The sectors made 120 revolutions per minute. By increasing the exposures to 1 minute or more, sometimes to 10 minutes, and through repeated observations, this source of error was largely eliminated. A slit opening of 0.015 mm. was uniformly used. This corresponds with an interval of 3.5 Ångström units on the plate at 5500 Ångström units and of 0.3 Ångström units in the far ultra-violet.

The plates were read in a dimly lighted room by holding them above an illuminated white background and comparing the spectral pairs through a slit in a card, this slit being from 20 to 40 Ångström units wide (referred to 5500 region). In the visible region final readings were usually made through the smaller slit.

In the ultra-violet a larger slit was used sometimes which measured in width from 5 to 20 Ångström units. The wave-length position was read off at the center of the slit from the wave-length scale held in position on the plate at the spectrum in question.

Solutions.

The oxyhemoglobin, carbon monoxide hemoglobin, and acid hematin solutions were prepared by the dilution of human blood, usually my own. The diluting fluids were 0.1 per cent sodium carbonate, freshly prepared, 0.4 per cent ammonia water, and 0.1 N hydrochloric acid. For the preparation of carbon monoxide hemoglobin, the solution in the ammonia flask was immediately saturated with illuminating gas. The blood was drawn with a recalibrated Record syringe from a vein, and equal volumes were added to each of the fluids in the proportion 1 : 100. The estimation of hemoglobin content of the blood was then made on the material in the hematin flask and further dilution to about 1:200 made accordingly. The estimation of hemoglobin content was made on a colorimeter (20) using an artificial color match for hematin. The error in thus preparing the various solutions used from time to time so as to be of the same relative concentration was not large. It was eventually compensated for. In the case of the visible portion of the oxyhemoglobin absorption this was in part done by reducing each set of data to a uniform level through correcting it to correspond to a certain fixed extinction coefficient at the bottom of the α-band. The data for the visible portion of the acid hematin absorption were all obtained in a short interval of time and the errors as between the different solutions were small.

After the various portions of the absorption curves were determined they were corrected for relative concentrations and checked at various points by using solutions made up from blood of known oxygen capacity. The oxygen capacity of fresh oxalated human blood was determined by the method of Van Slyke (21) and simultaneously a 1 : 200 dilution made with the various diluting fluids, all glassware being recalibrated. The carbon monoxide absorption curve was wholly determined from two such solutions. It would have been easier and better to have had such material

for the determination of the other two curves. It was believed that in a complete redetermination an almost prohibitive amount of labor would have to be expended before changes in the curves as already computed would be justified. Certain corrections were however made. The question of absolute concentration of the solutions in gm. per liter will be considered later.

Oxyhemoglobin, when oxygen saturation has been reached, and carbon monoxide hemoglobin, when kept saturated with the gas, form under these circumstances true solutions, which, when kept cold, remain stable for at least a week, and probably for a month or more.

The acid hematin as thus prepared acts for the present purpose as if it formed a true solution. After several months particles settle out which thereafter cannot be brought again into stable suspension. This process is accelerated if the material is kept at room temperature and is most apparent in very dilute solutions. In case the hematin mixture is somewhat more concentrated than $\frac{1}{50}$ blood dilution, some particles settle out almost immediately. Under the above conditions of preparation the hematin solution assumes in an hour a spectrophotometric condition which remains nearly constant for several days and even for several weeks.

Relation of Time to Color Depth of Acid Hematin.

It is known (22) that the hematin solution does not assume its full depth of color immediately. In order to determine just how rapidly it does develop its full color depth we made readings on ten preparations of acid hematin from the bloods of as many individuals. The first set of readings was made during the 3rd minute after the preparation of the hematin, the second set during the 15th minute, another during the 30th minute, and a last set on the following day. As a result of a long previous experience I was able to assume that the solution had reached a stable condition within 24 hours. The most careful spectrophotometric determinations have not shown any demonstrable increase in color depth within the next 10 days. All readings were therefore calculated as percentages of these final values and averaged. It seemed reasonable to assume that the rate of formation of acid

hematin should be a rectangular hyperbola of the general form $xy = -c$, when x measures the time in minutes and y is the per cent by which the acid hematin falls short of its full color depth. Using the value for y corresponding to 30 minutes for x, the constant c of the equation is determined as 40. The values of y for 3 minutes and 15 minutes fit the curve given by the value of c very closely, justifying the assumption that the curve has the form of a hyperbola. Hence the equation for the color density of a newly prepared acid hematin solution is $xy = -40$, where x is the time in minutes and y the percentage short of full color. A graph (Curve D) of this equation is included among the curves of Fig. 2, the squares of the figure being ten units each.

The further trial was made of following a specimen through from 1 to 40 minutes, making readings continuously and averaging them by tens. The points so obtained lay very closely on the curve.

It will be seen that in 20 minutes $y = -2$ and in 40 minutes $y = -1$. In other words, the specimen then has reached 98 and 99 per cent respectively of its full density. It will also be seen that if the specimen is read in 2 minutes the density falls short 20 per cent, or is 80 per cent of the final figure.

The equation not only shows how rapidly the solution reaches its full density, but what correction should be added to a reading when it is made early.

Observations.

The ultra-violet portion of the acid hematin curve was determined from eight plates made on the bloods of four individuals. The sectors were set for variations of tenths in extinction coefficients. The various plates differed only slightly from each other. The data given are a mean of those derived from five plates of my own blood.

For the visible portion of the acid hematin curve seven plates were made using my own blood and with such settings that the extinction coefficient varied by hundredths. Three of the plates were made on the day the solutions were prepared, the others on the 2 following days. The plates were all consistent. They were read, their points plotted, and a mean curve was drawn

through the locus. The discrepancies ran not over 2 per cent on either side of this curve. The plates were again read to eliminate errors of judgment and the mean of the new locus was taken as the true curve, the discrepancies with two or three exceptions having become less than 1 per cent.

Determinations of the ultra-violet absorption of oxyhemoglobin were made on the same bloods as those used for acid hematin, ten plates being made. They showed variations in the region 3200 to 4300 Ångström units, which were not then understood. Some of the solutions showed transmissions in the region 3200 to 3800 Ångström units, which corresponded to extinction coefficients as much as 15 per cent greater than those given. The great ultra-violet band fell short of its full depth by similar amounts. It would seem that these variations were due to incomplete oxygenation of the hemoglobin.

Oxygenation resulting in the dilution of venous blood would require at the most 1 cc. of oxygen per liter of solution. At room temperature, water contains about 6 cc. of dissolved oxygen, and the oxyhemoglobin solution made therefrom would soon come into equilibrium with the atmosphere. In recently distilled water, equilibrium would be less readily established. It is probable that in the discrepancies observed solutions using freshly distilled water were not sufficiently shaken. The effect of blood plasma present in the proportion of about 1:200 will be discussed later.

The ultra-violet portion of the oxyhemoglobin curve as obtained from certain apparently satisfactory plates was further checked on plates made from thoroughly oxygenated blood of known oxygen capacity. The form and depth of the curve at the great ultra-violet band centering on 4140 Ångström units was determined on solutions $\frac{1}{4}$ and $\frac{1}{10}$ as dense as those otherwise used. Here the curve was likewise carefully checked and discrepancies were small when the oxygen saturation was to be considered as satisfactory.

The visible portion of the oxyhemoglobin curve was at first determined from fourteen plates with my own blood. Except for short portions of the steep slopes of the curve the settings for extinction coefficients varied by hundredths. The plates having been correlated on the basis of the readings for the ex-

tinction coefficients at the maxima and minima points of the curve, all the plates were then read and their points plotted, the whole was rechecked for errors in judgment, and a curve was drawn through the locus. The discrepancies were somewhat less than those obtained in the visible portion of the acid hematin curve. The small extinction coefficients for the high transmission in the red were determined from the data of six plates, and the results checked by making readings with double the concentration.

The critical points of the curves for oxyhemoglobin and acid hematin, both in the ultra-violet and in the visible, were now checked on solutions of known oxygen capacity. About twenty plates in all were made for this purpose. They served at the same time to give data for the determination of the absolute concentration of the solutions to which the curves corresponded.

Incomplete data for the visible portion of the oxyhemoglobin curve had previously been obtained on a spectrophotometer at the physical laboratory of the United Gas Improvement Company. This was a Hilger quartz monochromatic illuminator coupled with a potassium photoelectric cell and galvanometer. A set of readings obtained with this apparatus for the region 4300 to 6000 Ångström units is consistent with that obtained by the photographic method except that the transmissions at the α- and β-bands, particularly the former, are not so low as they should have been. The dispersion of the instrument was too small for the purpose, and the slit width of 0.075 mm. used was too large. The blue and violet portion of the curve is, however, very closely checked and, as could be expected, the height of the α-β-peak was correctly observed.

I had originally made a determination of the absorption curves of oxyhemoglobin and acid hematin on a visual polarization spectrophotometer at the physical laboratory of the Corning Glass Works. These data were incorrect, the discrepancy being accounted for on the supposition of an error in the zero adjustment of the instrument. In order to check this point Dr. J. T. Littleton, Jr., of that laboratory, has made two redeterminations of the oxyhemoglobin curve on iced material which I sent him. His observations are consistent with my data as they now stand.

The absorption curve for carbon monoxide hemoglobin was obtained from the data of about ten plates made on two solutions

of known oxygen capacity. Only the Nernst lamp was used as a source and the ultra-violet absorption determined out to a little beyond 3100 Ångström units. The depth of the great ultra-violet band was determined on solutions $\frac{1}{10}$ as dense as those otherwise used. It was noticed here too that there were variations in the depth of this band, amounting in a week to a 20 per cent decrease in extinction coefficients for an iced specimen which had been opened several times. The band was brought back to its original depth by again passing illuminating gas through the solution. The height of the peak at 3760 Ångström units decreased likewise very considerably and was as easily restored. Changes in the visible absorption were small if present. The data are derived from freshly gassed solutions.

Concentration of the Solutions.

The concentration of the solutions here used may be calculated from the absorption constants as determined by Hüfner, Cherbuliez, de Saint Martin, Bardachzi, and Butterfield. To do this I calculate from my curve a mean e for the spectrum interval as used by the author in question. The product of this mean e and the author's constant gives a figure for the density of my solution. It happens that the mean e is very nearly equal to the e corresponding to the average transmission for the interval. The data are given in Table I.

If we disregard Butterfield's figures, the concentration would seem to be about 0.85 gm. per liter. As will be seen, however, Butterfield's figures are the correct ones. There is another very direct way of arriving at the concentration of the solutions used, through the determination of the oxygen capacity of the blood used.

Barcroft (23) shows that oxygen combines with hemoglobin in the ratio of one molecule of oxygen to one atom of iron, and further that there is one atom of iron in the hemoglobin molecule. If we accept this proposition, there remains only the question as to what is the percentage of iron in the hemoglobin molecule; what is the molecular weight of hemoglobin? There is very little discrepancy in the figures given by different authors for the iron content of hemoglobin. The accepted figure is about 0.335 per

cent (24). On the basis of this figure the oxygen capacity is 1.34 cc. per gm. of hemoglobin. This figure for oxygen capacity is subject to one correction. It is a maximum figure. Barcroft

TABLE I.

Concentration Data for My Oxyhemoglobin Solutions Based on Regions and Constants of Various Authors.

Author.	Region.	Constant.	Mean *e*.	Concentration.	Ratio.
Hüfner	α–β	2.070	0.411	0.85	1.54
"	β	1.312	0.633	0.83	
Cherbuliez	α–β	2.038	0.418	0.851	1.577
"	β	1.326	0.659	0.872	
de Saint Martin	α–β	2.153	0.419	0.90	1.556
" " "	β	1.330	0.651	0.865	
Bardachzi	α–β	2.094	0.411	0.86	1.54
"	β	1.334	0.633	0.843	
Butterfield	α–β	1.87	0.409	0.764	1.58
"	β	1.18	0.646	0.762	
"	5460	1.25	0.61	0.763	
"	5770 5790	1.096	0.688	0.754	

(23) has shown that the dissociation curve of hemoglobin (the oxygen saturation curve) has the formula

$$\frac{y}{100} = \frac{Kx^n}{1 + Kx^n}$$

where y is the percentage saturation of the hemoglobin with oxygen, x the oxygen pressure in mm. of mercury, n a number 2.5, and K a constant which varies slightly with normal individuals, averaging about 0.0003.

In measuring oxygen capacity the blood was saturated by spreading it thinly over the inner surface of an open, slowly rotating, conical, separatory funnel. The funnel was so rotated for about 10 minutes before pipetting off the specimen to be examined.

At atmospheric pressure the oxygen pressure is about 180 mm. of mercury. Substituting this figure for x in the formula, y becomes 99.2 per cent. The figure for the cc. of oxygen in 1 gm. of hemoglobin under the above conditions is therefore

$$\frac{99.2}{100} \times 1.34 \text{ cc.} = 1.33 \text{ cc.}$$

Accordingly a 1:201 dilution was made in the various solvents from blood whose oxygen capacity was being determined. The concentration of the solution thus produced when expressed in gm. of oxyhemoglobin per liter was equal to $\frac{10}{201 \times 1.33}$ times the figure for the oxygen capacity of 100 cc. of the whole blood. Extinction coefficients derived from such solutions of known concentration were used to ascertain the concentration of the solutions for which the original absorption curves had been determined. This was accomplished by making use of the fact that the ratio of corresponding extinction coefficients of any two solutions of a substance is equal to the ratio of their concentrations. If the extinction coefficients are known in each case, the concentration of one solution can be deduced from that of the other.

Eight plates were made from four oxyhemoglobin solutions of known concentration. The extinction coefficients at the bottoms of the α- and β-bands as computed from these plates were compared with the figures 0.713 and 0.67 obtained for the corresponding extinction coefficients of the oxyhemoglobin curve. The concentration of this original oxyhemoglobin solution as thus computed at the α- and β-bands was respectively 0.758 and 0.759 gm. per liter. The height of the peak between these two bands as had been computed for Table III was then slightly changed (from 0.408 to 0.406) so as to correspond to a concentration of 0.7585 gm. per liter when similarly referred to the average readings of these eight plates.

If we give these two figures for concentration as derived at the bands an equal weight with the concentration figures of Table I due to Butterfield, we obtain an average of 0.75975 or 0.76 as the gm. per liter of oxyhemoglobin in the solution to which the curve corresponds.

In the case of acid hematin the extinction coefficient of these known solutions at the nearly level interval 5500 to 5580 Ångström units was determined as the average of about a dozen consistent readings to be 0.5185 when computed for a 0.76 gm. solution. The extinction coefficients for the visible absorption of acid hematin were then all multiplied by such a factor as to bring the average extinction coefficient in the region 5500 to 5580 Ångström units to 0.5185.

The values of the extinction coefficients at the tops of the peaks at 3100 Ångström units were in the case of both curves, oxyhemoglobin and acid hematin, such as to correspond to a 0.76 gm. solution. The ultra-violet portion of these two curves was therefore not corrected further for density. The mid-ultra-violet portion of the oxyhemoglobin curve was corrected for oxygen saturation. The extinction coefficients as determined from the carbon monoxide hemoglobin plates, being determined from solutions of known oxygen capacity, were simply reduced by 8.5 per cent so as to correspond to a 0.76 gm. solution.

The intervals chosen by the various authors for the determination of the spectrophotometric constants are too wide. New intervals having a width of 40 Ångström units might be chosen so as to be centrally located. On the basis of the data herein contained such a set of constants for oxyhemoglobin would be as follows:

Oxyhemoglobin.

$A_0 = 1.87$ (5580 to 5620 Ångström units)
$A'_0 = 1.14$ (5390 " 5430 " ")
$A''_0 = 1.068$ (5740 " 5780 " ")

Carbon Monoxide Hemoglobin.

$A_c = 1.343$ (5540 to 5580 Ångström units)
$A'_c = 1.128$ (5360 " 5400 " ")
$A''_c = 1.128$ (5680 " 5720 " ")

Acid Hematin.

$A_h = 1.465$ (5500 to 5580 Ångström units)

Tables II, III, and IV give the absorption data for acid hematin, oxyhemoglobin, and carbon monoxide hemoglobin in an esti-

mated density corresponding to 0.76 gm. to the liter of oxyhemoglobin and in a layer 1 cm. thick.

In Fig. 1 which gives the data of Tables II to IV, extinction coefficients are converted into transmissions, the extinction coefficients being the cologarithms to the base 10 of the transmissions.

TABLE II.

Extinction Coefficients for Acid Hematin Corresponding to 0.76 Gm. of Oxyhemoglobin per Liter.

Wavelength.	Extinction coefficient.	Wavelength	Extinction coefficient.	Wavelength.	Extinction coefficient.	Wavelength.	Extinction coefficient.
Å. u.		*Å. u.*		*Å. u.*		*Å. u.*	
2410	2.06	3340	1.4	4950	0.655	5800	0.349
2440	1.8	3400	1.57	5000	0.625	5840	0.315
2460	1.7	3460	1.74	5040	0.61	5865	0.3
2480	1.65	3500	1.85	5070	0.6	5905	0.28
2540	1.59	3540	1.93	5140	0.59	5960	0.26
2600	1.64	3600	2.0	5200	0.588	6030	0.24
2645	1.7	3680	2.05	5260	0.587	6080	0.23
2670	1.74	3760	2.06	5300	0.583	6140	0.222
2720	1.8	3900	2.0	5320	0.58	6200	0.215
2780	1.81	4000	1.94	5360	0.567	6260	0.2125
2830	1.74	4065	1.9	5400	0.548	6300	0.214
2860	1.64	4100	1.88	5420	0.54	6340	0.22
2870	1.6	4200	1.81	5450	0.53	6400	0.24
2890	1.5	4300	1.73	5480	0.522	6460	0.265
2910	1.4	4390	1.63	5500	0.52	6520	0.29
2930	1.3	4440	1.56	5550	0.5185	6560	0.3
2960	1.19	4500	1.45	5580	0.516	6620	0.305
3000	1.07	4560	1.32	5600	0.5125	6660	0.3
3050	0.98	4600	1.23	5640	0.5025	6700	0.285
3100	0.96	4650	1.125	5660	0.494	6730	0.265
3170	0.99	4710	1.0	5680	0.48	6760	0.24
3210	1.07	4760	0.91	5700	0.459	6800	0.205
3230	1.12	4800	0.84	5720	0.43	6850	0.17
3260	1.19	4860	0.75	5740	0.409	6900	0.14
3300	1.3	4900	0 7	5770	0.375	7000	0.11

TABLE III

Extinction Coefficients for Oxyhemoglobin, 0.76 Gm. per Liter.

Wave-length.	Extinction coefficient	Wave-length.	Extinction coefficient.	Wave-length.	Extinction coefficient.	Wave-length.	Extinction coefficient.
Å. u.		*Å. u.*		*Å. u.*		*Å. u.*	
2450	2.06	3780	1.25	4750	0.37	5680	0.465
2460	2.0	3800	1.33	4800	0.335	5690	0.5
2480	1.9	3830	1.5	4840	0.31	5700	0.545
2520	1.81	3860	1.75	4920	0.27	5710	0.6
2590	1.77	3890	2.05	4960	0.255	5720	0.655
2660	1.81	3960	3.0	5070	0.233	5730	0.695
2760	1.87	4000	3.7	5120	0.24	5740	0.708
2830	1.81	4040	4.5	5160	0.26	5760	0.713
2870	1.7	4080	5.4	5200	0.295	5770	0.712
2895	1.6	4140	5.7	5240	0.365	5780	0.705
2910	1.52	4200	5.3	5270	0.44	5790	0.665
2930	1.4	4220	4.6	5280	0.462	5800	0.595
2950	1.3	4240	4.0	5300	0.51	5810	0.515
2970	1.2	4260	3.4	5320	0.553	5820	0.465
2985	1.1	4280	2.9	5330	0.58	5830	0.4
3010	1.0	4300	2.5	5340	0.6	5840	0.36
3050	0.9	4330	2.0	5360	0.638	5860	0.265
3100	0.882	4350	1.75	5380	0.66	5880	0.195
3140	0.898	4370	1.5	5400	0.668	5900	0.14
3200	0.98	4400	1.25	5415	0.67	5950	0.087
3230	1.04	4420	1.1	5430	0.667	5960	0.08
3270	1.12	4435	1.0	5440	0.66	5980	0.07
3330	1.21	4450	0.9	5460	0.61	6055	0.05
3400	1.254	4475	0.8	5470	0.58	6140	0.04
3460	1.262	4510	0.7	5480	0.55	6200	0.0355
3520	1.243	4540	0.63	5500	0.495	6300	0.0325
3580	1.155	4570	0.57	5520	0.45	6400	0.03
3600	1.112	4600	0.52	5550	0.42	6500	0.0295
3680	1.065	4650	0.46	5600	0.406	6600	0.0285
3740	1.125	4680	0.43	5650	0.42	6700	0.0275
3760	1.175	4710	0.4	5670	0.445	6800	0.0268

TABLE IV.

Extinction Coefficients for Carbon Monoxide Hemoglobin, 0.76 Gm. per Liter.

Wave-length.	Extinction coefficient.	Wave-length.	Extinction coefficient.	Wave-length.	Extinction coefficient.	Wave-length.	Extinction coefficient.
Å. u.		*Å. u.*		*Å. u.*		*Å. u.*	
3000	0.81	4080	4.15	4720	0.347	5660	0.658
3040	0.73	4100	4.9	4760	0.33	5680	0.671
3100	0.7	4120	6.0	4800	0.316	5700	0.675
3160	0.745	4130	6.7	4880	0.299	5720	0.671
3200	0.835	4140	7.4	4980	0.289	5730	0.664
3240	0.96	4150	8.0	5040	0.3	5740	0.645
3280	1.083	4160	8.45	5100	0.34	5760	0.575
3340	1.215	4190	8.7	5150	0.393	5770	0.533
3400	1.3	4220	8.44	5200	0.46	5790	0.445
3460	1.333	4230	8.0	5260	0.55	5820	0.325
3520	1.295	4240	7.3	5300	0.61	5840	0.259
3560	1.215	4250	6.5	5320	0.64	5860	0.213
3590	1.1	4260	5.65	5340	0.66	5900	0.164
3620	0.99	4280	4.25	5360	0.671	5950	0.131
3660	0.89	4300	3.0	5380	0.675	6000	0.111
3700	0.825	4320	1.9	5400	0.673	6040	0.1
3760	0.795	4340	1.4	5420	0.665	6140	0.08
3810	0.82	4360	1.1	5440	0.647	6220	0.07
3840	0.89	4380	0.9	5460	0.6125	6360	0.06
3860	0.985	4400	0.8	5480	0.6	6500	0.054
3880	1.1	4440	0.652	5500	0.581	6600	0.052
3900	1.38	4500	0.535	5550	0.565	6700	0.05
3960	1.9	4560	0.461	5600	0.58	6800	0.049
4000	2.4	4600	0.422	5620	0.6	6900	0.048
4040	3.05	4660	0.379	5640	0.63	7000	0.048

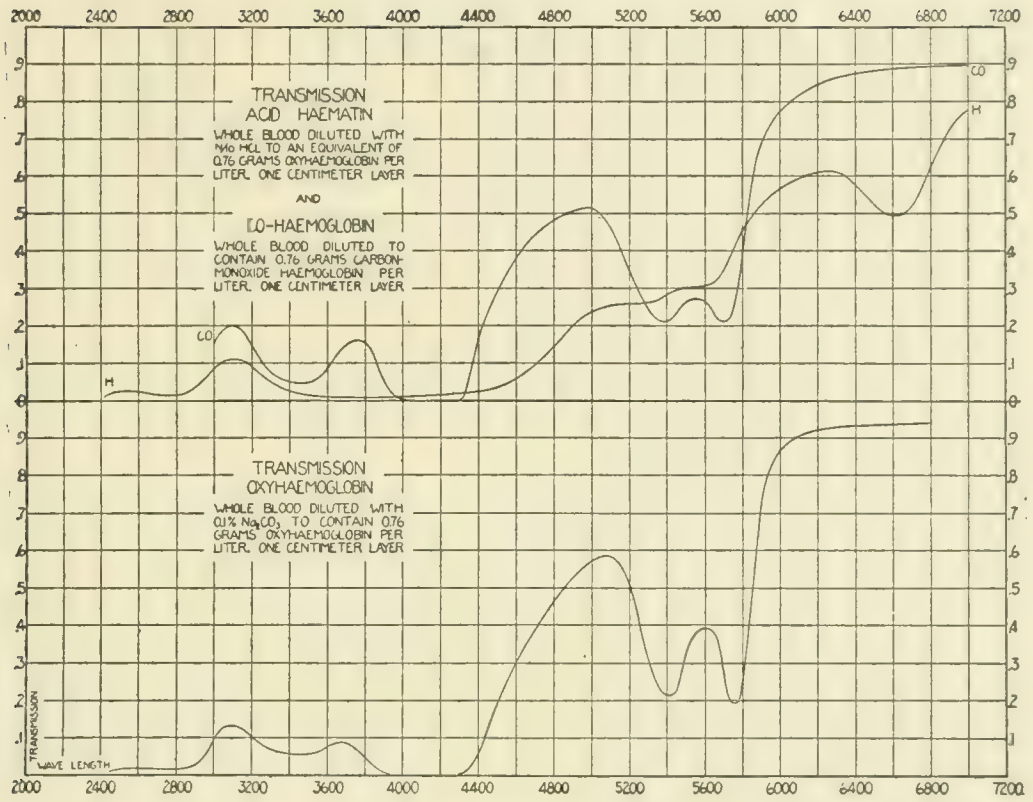

FIG. 1.

DISCUSSION.

Acid hematin is known to have different spectral characteristics under varying conditions as to acid and solvent (4, 5). The curve for material prepared in the manner described is constant and stable, for several days at least. The curve agrees essentially with the spectrogram by Rost, Franz, and Heise (4) of acid hematin prepared in a similar manner and with 1 per cent HCl. The prominent band in the red has its deepest point at about 6620 Ångström units. The difficulty experienced by many (4) in distinguishing photographically the other two bands in the visible is readily understood. They are very shallow. There is a broad general depression extending from 5100 to 5900 Ångström units which is divided by a very slight rise at 5480 Ångström units. In the curve this shows up very distinctly but in a single spectrogram it is discernible only with difficulty, if at all. It first becomes apparent when quantitative absorption measurements are

made. This rise appeared both by the photographic method and with the visual spectrophotometer at Corning.

The great ultra-violet band of acid hematin is broader and shallower than in the case of oxyhemoglobin, the broadening extending it further into the ultra-violet and obliterating the small peak at 3680 Ångström units which appears in the oxyhemoglobin curve. There is beyond the peak at 3100 Ångström units a shallow but distinct band with its center at 2780 Ångström units. Beyond 2400 Ångström units the absorption becomes very great, more rapidly so than in the case of oxyhemoglobin. The further side of this band does not appear within the range of the instrument (2050 Ångström units).

The β-band of oxyhemoglobin is seen to be fainter than the α-band, the difference in depth being, however, slight. As viewed in the ordinary spectroscope there is a subjective difference greater than the real difference. The great ultra-violet band is much deeper, the ratio of the extinction coefficients being about eight. This means that the ultra-violet band can be recognized in eight times as dilute a solution as can the visible bands. A quartz spectrograph is almost necessary.

Oxyhemoglobin has two further bands in the ultra-violet, at 3460 and at 2760 Ångström units separated by a peak at 3100 Ångström units somewhat higher than the corresponding one of acid hematin. The similarity in the ultra-violet of the absorption of the two substances would seem to indicate that it is due in large part to a radical common to both. In fact, this similarity persists, to a less extent, in the visible.

Carbon monoxide hemoglobin has an absorption similar to that of oxyhemoglobin. The differences are interesting; in the visible there is a reduction in the amplitude of the curve, the bands are not so sharp, and the transmission is not so great, particularly at the peak between the α- and β-bands. It is the lowness of this peak which principally accounts for the difference in shade between solutions of the two compounds. The visible bands of carbon monoxide hemoglobin are approximately of the same depth as the β-band of oxyhemoglobin; they are shifted with respect to those of oxyhemoglobin toward the violet; the great ultra-violet band is much deepened and shifted in the contrary direction. In the ultra-violet, the two peaks are higher than in the

case of oxyhemoglobin. The height of the peak at 3760 Ångström units and the depth of the band at 4190 Ångström units decreases very markedly with loss of carbon monoxide from the solution, a change which also holds for oxyhemoglobin.

According to Lewis (25) beyond 3100 Ångström units serum shows a rapidly increasing amount of absorption which reaches a maximum at about 2800 Ångström units, the next minimum being at 2540 Ångström units. The forms of the acid hematin and oxyhemoglobin curves in this region are probably due to the serum present in an approximate dilution of 1:200. In particular the peak at 2540 Ångström units would seem to be due to this. The amount of the extinction due to the admixed serum is only from one-fourth to one-seventh of the whole.

A 1 cm. layer of undiluted blood serum has an absorption which in the red part of the spectrum amounts to an extinction coefficient of about 0.2. This extinction increases uniformly across the visible spectrum to reach a value of about 0.7 in the blue. From the ultra-violet border out to 3200 Ångström units the extinction coefficient of serum is approximately 1. It varies probably with the food taken. I have observed the extremes of 0.8 and 1.7.

In a dilution of 1:200, therefore, serum has an extinction varying from 0.001 to 0.004 in the visible spectrum, being only 0.0015 at its middle point. These figures added to, or subtracted from the extinction coefficients of the hemoglobins do not change them appreciably. The presence of the plasma can therefore be neglected in discussing the visible absorption of these compounds.

The oxyhemoglobin curve as given is approximately that due to a layer of whole blood 0.05 mm. thick. Such a layer is equivalent to a layer of red blood cells in heterogeneous position nine thick, or in rouleau, fifteen thick.

The blood in the superficial capillaries of the skin would therefore be sufficient in quantity to absorb almost completely all the violet and ultra-violet light which might fall upon it. This absorption is particularly intense in the neighborhood of 4200 Ångström units.

Hemotometry.

The banding in the visible of solutions of these three compounds makes it extremely difficult to secure artificial color matches for them. It would be desirable to find an artificial

material whose absorption curve coincided throughout with that of one of them. Under such circumstances the match would appear perfect in any light and to any eye. As the absorption curve of the material to be used as a match deviates more and more from that of the blood preparation, factors are introduced which make it exceedingly difficult to predict from the curves the character which the match will assume.

That a match then exists at all is due to physiological conditions, to the fact that the sum of two colors gives to the eye an impression of a third, a mixed color.

Thus a piece of glass transmitting only green and orange light would in daylight appear to have the same color as a piece of glass transmitting yellow light. But if pure spectral green light were used as an illuminant, the one glass would appear green, the other would be opaque. The two substances may thus appear to have the same color without their absorption curves being at all alike. If their absorption curves are alike, or nearly so, they will appear to have the same color under widely varying conditions, both as to observer and illumination. It is thus essential in order that a color match be satisfactory under varying conditions that the absorption curves of the two substances composing the match be as near alike as possible.

The similarity must be greatest in the region of maximum luminosity, a region whose middle point in the case of ordinary white light is 5560 Ångström units (26). Toward the two ends of the visible spectrum the luminosity is so small that discrepancies here do not materially affect the impression on the eye.

The Miescher hemoglobinometer uses as a match for oxyhemoglobin a gold ruby glass. This glass has a broad absorption band with its center at 5200 Ångström units, which in general balances the two absorption bands of oxyhemoglobin. The transmission of this glass in thickness corresponding to the oxyhemoglobin solution of 0.76 gm. to the liter is given in the upper part of Fig. 2, Curve A. Its absorption only roughly approximates that of oxyhemoglobin. That a match exists at all is, so to speak, accidental, and then only under fixed conditions of illumination.

The upper portion of Fig. 2 contains two other curves, B and C, obtained by multiplying the transmission curves of the Miescher glass and of oxyhemoglobin respectively by the visibility curve

for the Hefner lamp, whose luminosity values are very similar to that of the candle. These two modified curves might be called the physiological transmissions of the two materials. They represent the actual appearance to the eye of each of the two materials when illuminated by the candle. The transmissions of the glass and of the oxyhemoglobin at each point of the spectrum are decreased at each point to correspond to the actual impression which the transmitted light produces on the eye.

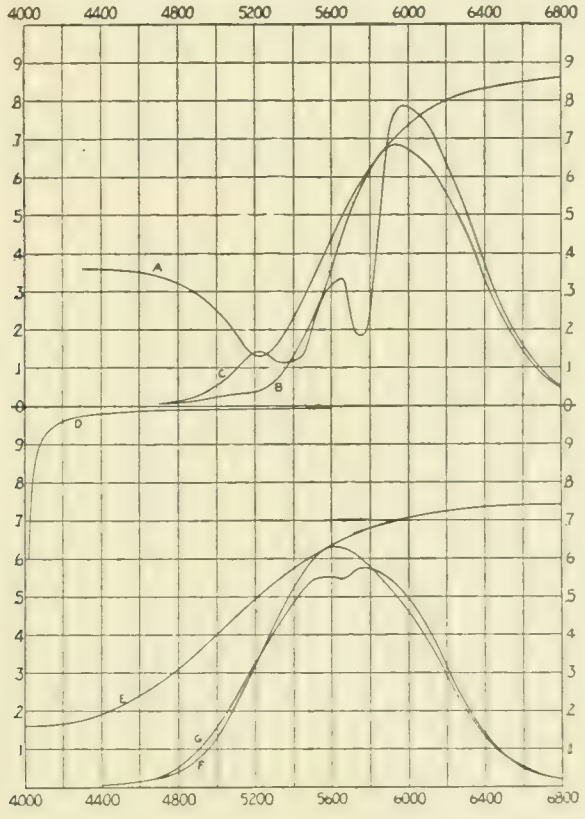

FIG. 2. Curve D is a plot of the equation $xy = -40$, the abscissæ representing time in minutes and the ordinates the percentage short of full color of an acid hematin solution, the squares being each 10 units. For the other curves the ordinates represent transmissions in tenths and the abscissæ wave-lengths in Ångström units. A is the Miescher glass in a thickness corresponding to the oxyhemoglobin of Fig. 1. B is the same multiplied by the visibility of the Hefner lamp. C is the oxyhemoglobin curve multiplied in the same manner. E is the transmission of 1 mm. of high transmission yellow colorimeter glass. F is the same multiplied by the visibility of white light. G is a corresponding acid hematin transmission so multiplied. It is assumed that there is a sufficient intensity of illumination to make applicable the visibility values used.

The amount of agreement or disagreement between these two physiological transmission curves gives an interpretation of the quality of the match. The area under each curve represents the quantity of light which each material appears to transmit. The two areas are equal, the light fields being presumed to balance.

There does not seem to be any way to improve on this match for oxyhemoglobin. There is no red glass that falls to zero transmission near 5800 Ångström units. They all come down to zero much further in the red, presenting a distinctly different hue. It is possible by using an illuminant that is entirely red to confine the problem to the level portion of the high transmission red part of the oxyhemoglobin curve. Then the shades match exactly, but the transmission of the oxyhemoglobin is there so high and the sensitivity of the eye in the middle and far red so low that it is impossible to distinguish any but gross differences in color. The same situation exists in the case of carbon monoxide hemoglobin, except that its relatively low peak between the two visible bands makes it possible to seek a glass whose single band will coincide with the position of this peak. Unfortunately glasses having high transmissions in the blue and red have their central bands too far over in the green. In the case of acid hematin the situation is better.

I have examined at the laboratory of the Corning Glass Works a collection of about 1,000 colored glasses, representing the possibility of a million pairs. There is no glass or combination of glasses giving an absorption whose curve runs closely parallel to that of acid hematin. The "high transmission yellow" semaphore glass made by the Corning Glass Works, however, has an absorption curve which runs smoothly as a mean through the acid hematin curve. It has not been possible to combine this with any other glass so as to produce a combination having a curve more closely approximating that of the acid hematin than does the yellow glass alone.

This glass matches acid hematin best when to its specific absorption is added the flat absorption due to reflection losses at its surface. In colorimetric comparison, therefore, the yellow glass is not to be balanced by a corresponding piece of clear glass, but is to be used alone on one side of the color balance. The hematin solution is, however, to be balanced for reflection

losses at its surface by clear water on the colored glass side of the balance.

This glass in thickness of about 1 mm. is a very close match for acid hematin and the discrepancy between its curve and that of the acid hematin is sufficiently small so that the match does not perceptibly vary with individuals. In this thickness the depth of color is about an optimum for judging differences of color depth.

Curve E, Fig. 2, gives the transmission of a piece of this glass 1 mm. thick. Curves F and G are the physiological transmissions of this glass and of a corresponding acid hematin solution respectively. They are obtained by multiplying the transmissions of the two materials by the luminosity curve for white light. It will be seen that they fall more nearly together than do the corresponding Curves B and C for the Miescher hemoglobinometer.

In order that the glass shall match a fixed density acid hematin solution the illumination must be constant. It may be either the light of a northern sky or that given by a nitrogen-filled tungsten lamp filtered through "daylite" Corning glass, the two illuminants being interchangeable. The match is sufficiently good so that further improvement is not a matter of importance, there being a limit to the refinement with which any colorimetric estimation may be made. The use of a fixed thickness of colored material as a standard has a distinct advantage over the use of a wedge. It is impossible to secure an artificial color match which shall run true through a range of thicknesses, though some may do so approximately.

Clinical Estimation of Oxyhemoglobin.

There is no method of estimating hemoglobin which is superior to the oxygen capacity method of Van Slyke (21). For clinical purposes, however, some colorimetric method for the estimation of hemoglobin is essential. It therefore becomes a question of devising a color standard which shall be permanent, which to different individuals shall have the same apparent hemoglobin value, and which can be easily supplied as a uniform product. A stock of "high transmission yellow" glass having the properties set forth in the previous section has been set aside for this pur-

pose.[2] Its hemoglobin value has been carefully estimated. It is to be used in thicknesses of 1 mm. in connection with some colorimeter of the Duboscq type. When used with the Duboscq colorimeter it is placed in the light path of one of the cells (at the top of the plunger) and the corresponding cell or cup is filled with water. In the other cup are placed 5 cc. of 0.1 N HCl (1 per cent C.P. HCl) and to the cup are added 20 c.mm. of blood obtained from a puncture wound with a capillary pipette.[3] If the two light fields are now balanced by lowering the plunger in the hematin cup the hemoglobin reading in gm. per 100 cc. of whole blood is represented by the quantity $\frac{0.38d}{t}$ where d is the dilution (in this case 251), t the thickness of the balancing solution in mm., the colorimeter reading, and 0.38 a number empirically determined for a 1 mm. glass.[4] This expression has to be modified

[2] The Arthur H. Thomas Company, Philadelphia, is prepared to supply this glass cut, ground, and polished to thickness, the thickness being engraved on each piece. They will also supply the necessary pipettes, and the "daylite" unit for use at night consisting of an 8″ roundel of "daylite" glass and an appropriate shade. The measured glass discs will also be provided as a part of the regular equipment of the new Bausch and Lomb colorimeter of the Duboscq type.

[3] The colorimeter described by Bock, J. C., and Benedict, S. R., (*J. Biol. Chem.*, 1918, xxxv, 227) is well adapted for this purpose. The colorimeter cup is small enough to be almost filled by 5 cc. of solution, thus permitting readings to be made on bloods running as low as 20 per cent of the normal without its being necessary to increase the density of the hematin solution by using a larger amount of blood. For the ordinary Duboscq cup the 20 c.mm. of blood suffice for hemoglobin readings down to 50 per cent of the normal.

[4] Since the thickness of the glass can seldom be exactly 1 mm., there is a further factor multiplying this formula. If h be the thickness of the glass, then for values of h sufficiently near unity it is permissible for this factor to be h itself. As a matter of fact it is slightly less than h. For such an approximation h should not vary from unity by more than 0.05 mm. The actual value of the factor is somewhat involved. If $\phi(\lambda)$, λ being wavelength, represents the values of the extinction coefficients for a 1 mm. glass alone (not including surface loss), then for the glass and surface together $e = \phi(\lambda) + 0.041$ and the transmission is $T = 10^{-\phi(\lambda) - 0.041}$ (Curve E, Fig. 2). The total energy transmitted by the glass in the visible region is the area under this curve, or

$$E = \int_{\lambda = 4000}^{\lambda = 7000} 10^{-\phi(\lambda) - 0.041}\, d\lambda$$

because of the fact that the hematin does not reach its full density for some time (as stated above). If x is the time in minutes after making the dilution from the pipette, then the reading is too small by a percentage equal to $\frac{40}{x}$, and the real reading is

$$\frac{38d}{t\left(100 - \frac{40}{x}\right)}$$

It will be seen that when x is very large this becomes equivalent to the first formula given. When x is equal to 10 (at the end of

But, as mentioned above, we are concerned rather with the physiological effect of this energy than with the energy itself. If the visibility of white light is represented by the function $\theta\ (\lambda)$, then this physiological energy impression or the luminosity of the illuminated glass is

$$P = \int_{\lambda = 4000}^{\lambda = 7000} \theta\ (\lambda)\ 10^{-\phi\ (\lambda) - 0.041}\ d\lambda$$

The thickness of the glass being h instead of unity, the new physiological transmission integral is

$$P_h = \int_{\lambda = 4000}^{\lambda = 7000} \theta\ (\lambda)\ 10^{-h\,\phi\ (\lambda) - 0.041}\ d\lambda$$

If $\psi\ (\lambda)$ represents the extinction coefficient of a solution of acid hematin matching the glass given by $\phi\ (\lambda)$, then a condition for the match is

$$\int_{\lambda = 4000}^{\lambda = 7000} \theta\ (\lambda)\ 10^{-\psi\ (\lambda)}\ d\lambda = \int_{\lambda = 4000}^{\lambda = 7000} \theta\ (\lambda)\ 10^{-\phi\ (\lambda) - 0.041}\ d\lambda$$

and this condition holding, then

$$\int_{\lambda = 4000}^{\lambda = 7000} \theta\ (\lambda)\ 10^{-h\,\psi\ (\lambda)}\ d\lambda \neq \int_{\lambda = 4000}^{\lambda = 7000} \theta\ (\lambda)\ 10^{-h\,\phi\ (\lambda) - 0.041}\ d\lambda$$

but the two integrals are nearly equal when h is nearly unity. No matter how nearly $\phi\ (\lambda)$ may equal $\psi\ (\lambda)$ these two latter integrals cannot be alike because of the factor $10^{-0.041}$ in one of them. If conditions are such that the surface factor $10^{-0.041}$ is absent then, since the assumption is that the functions $\phi\ (\lambda)$ and $\psi\ (\lambda)$ are not identical, it follows that the integrals also are not identical. They can be made equal for one and only one value of h, a value here chosen as unity. This inequality constitutes sufficient proof of the proposition that a wedge of glass can never exactly balance a varying solution density. The accompanying inequalities in shade constitute the most important difference.

10 minutes), the hematin has reached to within 4 per cent in 20 minutes to within 2 per cent, and in 40 minutes to within 1 per cent of its final value. For mental calculations the figure given by the simple formula $\frac{0.38d}{t}$ may therefore be simply increased by these percentages.

Table V gives some of the readings by which the calibration of the glass was made and indicates what latitude may be expected in such observations. The table gives results with the artificial illumination and with ordinary daylight. Each column represents ten settings made by the individual whose initials stand at the head of the column. The individuals making the settings were not aware of the readings until they had finished the experiment. It is impossible to expect any single setting to come very close to the mean. This is true of any sort of colorimetric setting though perhaps it is not generally recognized.

A formula giving the oxygen capacity of 100 cc. of blood is obtained by introducing the factor 1.34 into the above formula.

$$\frac{0.38d}{t} \times 1.34 = \frac{0.51d}{t}$$

Haldane and Smith (27) adopt 18.5 cc. oxygen capacity as a normal. The resultant hemoglobin percentage scale is known by his name. On his scale the formula for per cent hemoglobin is $\frac{2.75d}{t}$ per cent.

Tables VI and VII give in convenient form the figures into which t, the thickness of the balancing solution in mm., is to be divided in order to obtain the concentration of hemoglobin in gm. per 100 cc. of whole blood and in per cent Haldane. The dilution is taken as 251. To each of certain possible thicknesses of colored glasses there corresponds a column of figures corrected for the time factor in the formation of acid hematin.

TABLE V.

Colorimeter Readings Balancing a Certain Hematin Solution against Yellow Glass.

	H. S. N.	M. G. P.	H. S. N.	M. G. P.	H. S. N.	M. G. P.	H. S. N.	M. G. P.	H. S. N.	M. G. P.	Average.
Illumination with "daylite" unit.											
	4.05	3.9	4.05	4.2	4.0	3.8	4.0	4.05	4.0	4.0	48.60
	4.0	3.8	4.05	4.0	4.0	3.9	4.1	4.15	4.05	3.8	47.60
	4.0	4.15	4.1	4.15	4.1	4.1	4.0	4.15	3.95	3.9	48.35
	4.0	4.05	4.0	4.0	4.3	4.1	4.05	4.1	4.2	3.8	47.65
	4.05	4.0	4.25	3.8	3.9	4.2	4.15	4.1	4.2	4.2	48.05
	4.3	3.85	4.4	3.8	4.15	3.9	3.85	4.3	4.1	4.15	48.25
	4.05	4.05	4.1	4.1	4.4	4.1	3.95	4.1	4.0	4.1	47.40
	4.0	4.05	4.35	3.9	4.0	4.05	4.25	3.8	4.15	4.1	47.60
	4.25	4.15	4.05	3.9	4.0	4.15	3.95	3.95	4.15	4.1	47.90
	4.1	3.8	4.0	4.0	4.2	4.15	4.1	3.9	4.1	3.8	46.95
	40.80	39.8	41.35	39.85	41.05	40.45	40.40	40.60	40.90	39.95	478.35
Zero correction.	7.8	7.8	7.0	7.8	7.0	7.8	7.0	7.0	7.0	7.0	
	48.60	47.60	48.35	47.65	48.05	48.25	47.40	47.60	47.90	46.95	
Illumination with light of northern sky.											
	4.15	4.0	4.05	4.05	4.0	4.0	3.95	3.95	4.05	3.8	48.05
	4.05	3.9	4.0	3.8	3.9	4.2	3.95	4.0	4.0	4.0	47.50
	4.15	3.9	4.05	4.05	4.0	4.1	3.9	4.15	4.1	3.8	47.55
	4.2	3.95	3.9	4.0	4.0	4.0	3.9	4.0	4.1	4.05	47.00
	4.15	4.2	4.05	3.95	3.95	4.0	3.95	3.9	4.05	4.15	47.80
	4.0	4.2	4.0	3.95	4.0	4.0	3.9	3.85	4.1	4.15	48.40
	4.05	4.1	4.0	4.0	3.85	4.0	4.15	4.1	3.85	4.0	47.85
	4.0	4.05	4.05	4.1	4.05	4.0	4.05	4.0	4.1	4.15	48.15
	4.1	4.0	4.25	4.1	3.95	4.0	4.05	4.1	4.05	4.2	48.40
	4.2	4.2	4.2	4.0	4.1	4.1	4.05	4.1	4.0	4.2	48.50
	41.05	40.50	40.55	40.00	39.80	40.40	39.85	40.15	40.40	40.50	479.20
Zero correction.	7.0	7.0	7.0	7.0	8.0	8.0	8.0	8.0	8.0	8.0	
	48.05	47.50	47.55	47.00	47.80	48.40	47.85	48.15	48.40	48.50	

Average with "daylite" unit			478.35
" " light from northern sky			479.20
Final average	200	957.55	
			4.7877

Oxygen capacity of blood used ..... = 20.6 cc.
Dilution ..... = 201
Colorimeter factor ..... = 0.369
Thickness of colored glass ..... = 0.97 mm.
Colorimeter factor corrected to 1 mm. glass = 0.38

TABLE VI.

To obtain gm. of hemoglobin per 100 cc. of whole blood, divide the colorimeter reading into the figure of the appropriate square, the choice of the square depending upon the thickness of the glass used and the length of time since dilution of the blood was made.

Time since dilution.	Thickness of colored glass in mm.										
	0.95	0.96	0.97	0.98	0.99	1.00	1.01	1.02	1.03	1.04	1.05
min.											
10	94.4	95.4	96.4	97.4	98.4	99.4	100.4	101.4	102.4	103.4	104.4
15	93.1	94.1	95.0	96.0	97.0	98.0	99.0	100.0	101.0	102.0	103.0
20	92.5	93.5	94.5	95.4	96.4	97.4	98.4	99.4	100.4	101.3	102.3
30	91.8	92.8	93.8	94.8	95.7	96.7	97.7	98.6	99.6	100.5	101.5
40	91.6	92.5	93.5	94.5	95.4	96.4	97.4	98.3	99.3	100.3	101.2
Final.....	90.6	91.6	92.5	93.5	94.4	95.4	96.4	97.3	98.3	99.2	100.2

TABLE VII.

To obtain the per cent hemoglobin, Haldane scale, divide the colorimeter reading into the figure of the appropriate square, the choice of the square depending upon the thickness of the glass used and the length of time since dilution of the blood was made.

Time since dilution.	Thickness of colored glass in mm.										
	0.95	0.96	0.97	0.98	0.99	1.00	1.01	1.02	1.03	1.04	1.05
min.											
10	683	690	697	704	712	719	726	733	740	748	755
15	673	680	687	694	702	709	716	723	730	737	744
20	669	676	683	690	697	704	711	718	725	732	739
30	664	671	678	685	692	699	706	713	720	727	734
40	662	669	676	683	690	697	704	711	718	725	732
Final.....	655	662	669	676	683	690	697	704	711	717	724

CONCLUSION.

The transmissions of acid hematin, oxyhemoglobin, and carbon monoxide hemoglobin for the ultra-violet and visible spectra have been determined to within limits of error, which I believe do not exceed 4 and 2 per cent respectively. The quantitative data for the oxygen capacity of hemoglobin has been shown to agree essentially with certain spectrophotometric data and the two have been brought into correlation with each other and with the complete absorption curves of the three compounds. The optical

conditions underlying colorimetric hemotometry have been briefly discussed. A hemoglobinometer with a colored glass standard has been described.

I am indebted to many for the interest which they have shown in the experimental difficulties which have presented themselves. More particularly I wish to thank Drs. Littleton and Gage of Corning and Dr. Karrer of the United Gas Improvement Company for the facilities which they have extended to me.

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THE RELATION OF THE SECTOR OPENING OF THE SECTOR PHOTOMETER TO THE EXTINCTION COEFFICIENT

IN determining absorptions with a spectrograph and sector photometer it is necessary to know the relation existing between the sector opening and the extinction coefficient. If the two beams whose intensities are to be equalized by interposed sectors be donated by I and I' respectively, then

$$\log \frac{I}{I'} = e$$

defines e as the extinction coefficient of the substance for which I' is the transmitted beam and I the corresponding incident beam. If these two beams, I and I', be equalized photographically by means of interposed rotating sectors, S and S', then some relation exists between I/I' and S'/S.

A previous determination by H. E. Howe[1] of this relation made

$$\frac{I}{I'} = \frac{S'}{S}$$

where S is the variable sector cutting down the beam I till it balances the beam I'. The equality was established by measuring with a sector photometer the transmissions of neutral smoke-glass plates, the transmissions of which had previously been measured on a visual spectrophotometer.

In further establishing the validity of this equality the method here employed has been to use likewise two beams of known relative intensities determined geometrically as a function of the relative distances of their sources from the slit of the spectrograph.

Using the Hilger quartz spectrograph, size C, in front of one half of a slit 3 mm. long there was placed a total reflecting prism whose

[1] H. E. Howe, *Phys. Rev.*, VIII., 6, 1916, 674.

face was illuminated through a variable sector by a fixed Nernst lamp. The illumination of the other half of the slit was accomplished by another Nernst lamp arranged on a runway in the axis of the collimator so that its distance from the slit could be varied at will.

The lamps were on the same 110-volt alternating current, city circuit, and plates were always made under such conditions that the voltage did not vary more than two volts during the course of an experiment. The lamps being of the same construction it seemed reasonable to suppose that the simultaneous variations in candle power of the two lamps due to such slight variations in voltage would be equivalent.

A series of exposures were made on successive portions of a plate with the movable lamp set at distances increasing by small increments. Such a series of exposures would then be expected to contain one at which the illumination by the movable lamp would balance that by the fixed lamp as judged by equal blackening of the spectrum bands on the plate.

The average distance for such a balance with the sector at rest, as determined by making settings with increments of half a centimeter, was about 40 cm. It was possible to estimate the true distance to tenths of a centimeter. With the sector running corresponding settings of the movable lamp were made for various openings of the sector, the principal openings being 7.3°, 10° and 19°. The following table gives the results for these openings, the figures being all reduced to a common denominator by dividing the distance of the movable lamp from the slit by the initial distance at which the two beams balance with the sector at rest. The figures are arranged in rows according to the sector opening and in columns according to the individual plates and set ups of the apparatus.

The apparatus was taken down and realigned

matic error. Considerable care was taken to several times in order to eliminate any syste- have the spectrograph and runway level, and to

Sector	Distance Observations	Average	Theoretical $\frac{l}{l'} = \frac{S'}{S}$
19°	432, 432, 443, 439, 444, 437, 432, 436, 438, 441, 440, 440	438	435.4
10°	617, 596, 591, 596, 591, 610, 591, 600, 600, 614, 614	602	600
7.3°	712, 690, 695	699	702

have the runway so that the Nernst filament remained in line with the collimator axis. This was accomplished in some instances by

halving the distance between the two points at which the spectrum disappeared in shoving the lamp from side to side, and in some instances by placing the filament at one end of the runway in contact with the slit, at the other end making a symmetrical shadow of the collimator tube on the spectrograph body. The Nernst filament was placed vertically. It was used at such a distance from the slit that at its nearest position to the slit the whole of it was effective in illuminating the plate.

The graduations of the sector opening were compared and corrected with a protractor. The sector wheel ran 120 revolutions per minute, there being two openings in the wheel, the sum of the two being an angular opening equal to that given in the table.

The plates used were half of them Wratten & Wainwright Panchromatic and half Seeds Panchromatic. In one instance a Seeds Process was used with the same results. The plates were given uniform tank development. The exposures were such as to give rather faint images, necessary in order to judge accurately differences in intensity. The exposures were such, however, that with the sector running they were always longer than one minute. A plate would contain a set of exposures for the so-called zero of the experiment, the initial balance distance, and a set of exposures with the sector running, the movable lamp being placed at distances such as to make equivalent sets of exposures. The distances corresponding to the two pairs which matched on such a plate when divided the one by the other gives a quotient which is a figure of the table. With a good setting the two spectral bands balanced throughout if they balanced at all, showing that the proposition is independent of wave length.

As the sector photometer is used for spectrophotometry the two beams fall on a bi-prism in front of the slit with the result that the two

beams on the plate are in juxtaposition. Because of the fact that the total reflecting prism used here had been slightly ground on its edges the two bands of the pair in this experiment were .4 mm. apart, which increased somewhat the difficulty of judging equality in blackening. The error in such judgments was probably of the order of 2 per cent. It may have been less than this. The averages for the figures of the table differ as the last two columns show by about a half per cent. from what the figure should be if the diminution in the intensity of the beam due to the sector is photographically equivalent to the diminution due to a proportionate increase in distance.

That this equality exists is certainly a coincidence. Recently Helmick[2] has shown that long exposures produce less blackening than short exposures, the total energy being the same (this being when both the short and long exposure are longer than a certain fixed time). In some rough experiments which I first made I found that the total actual intermittent exposure necessary to produce equal blackening through a 72° sector was about of the order of 12 per cent. longer than for a like continuous exposure, *i. e.*, the sector at rest. The evidence herein contained goes to show that when the beam is dimmed by increasing the distance of its source the exposure must likewise be longer by this same amount. In other words, if B_1, B_2 and B_3 are the blackenings due respectively to a certain beam, to the same beam made intermittent and to a beam of decreased intensity, all of the beams delivering equal total energy through the regulation of the time factor, then B_2 and B_3 are less than B_1 but are equal to each other.

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[2] P. S. Helmick, *Phys. Rev.*, XI., 5, 1918, 372.

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THE FUNCTIONAL VALUE OF NEWLY FORMED CONNECTIVE TISSUE.

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Experimental tuberculosis, viewed broadly, presents a characteristic picture not to be confused with any other except that of the spontaneous or natural disease. Experiments devised to analyze the picture into its component parts have usually failed to develop information of decisive value. If, for example, parallel inoculations are made with living tubercle bacilli and with those killed by heat, the lesions produced are much alike in the beginning and remain so for some time. Finally, those due to the living bacilli are progressively reduplicated by the further invasion of the tissues, while those due to the dead bacteria are gradually healed. It is difficult again to say in what essential particular the lesions due to dead tubercle bacilli differ from those caused by other mildly irritant foreign bodies introduced into the tissues.

The lesions above mentioned have in common an initial acute inflammatory reaction and a subsequent deposit of more or less perfectly formed fibrous connective tissue. At the point of divergence this connective tissue in the case of the living tubercle bacillus undergoes degenerative changes; it is broken down. But this divergence in the type of reaction is not universal. With the living bacteria, wherever either locally or generally the infection is resisted or overcome the connective tissue develops more or less steadily until the products of the earlier inflammation are replaced. It then tends to be reabsorbed. If the mass is small it may completely disappear with time; if the mass is large it remains as a scar in no essential particular to be distinguished from a scar due to any other cause.

This reaction of the connective tissue, intimately associated as it is in favorable cases with the healing of tuberculosis, may in the abstract be viewed either as a process dependent in its entirety on other

factors in the disease or it may be considered to be a factor of prime importance in the recovery or partial recovery of the animal. Facts are lacking on which to base the adoption of one or the other of these concepts. For the purposes of this paper, and merely as a working hypothesis, we have adopted the view that the reactive qualities of the connective tissue may be the decisive factor in determining the outcome of a tuberculous infection.

In order to proceed from this point we require some knowledge not at present available of the connective tissue and its reactive possibilities. Is the connective tissue in this sense a constant or a variable for any species of animal? If connective tissue is to be held responsible for variations in reaction to the tubercle bacillus it can only be on the assumption that it has a variable capacity for reaction. Such an assumption is, of course, in accord with the presumption on the broadest biological principles, most, if not all, functions which can be measured being variants in either direction from a typical mean value. In the search for a measure of the capacity of connective tissue to react we have turned to the facts and experiments relating to the healing of wounds.

The repair of any solution of continuity of tissues other than the purely epithelial surfaces involves the production of connective tissue, and attempts have been made to study this reaction quantitatively, particularly, of recent years by Carrel and his associates.[1] A careful consideration of the conditions of these studies makes it seem unlikely that the values determined have any direct relation to the reaction of connective tissue.

As an example we may select an incised wound made through the skin into the soft parts and allowed to gape during the healing process. The gaping wound will fill with exudate which will then become organized with granulation tissue, and this will subsequently be replaced by connective tissue. When the gape or cavity has become well filled with granulations the epithelium will begin to cover the wound by extension from the margins. It is the rate of growth of the epithelium which has been the subject of the quantitative studies above mentioned. Granted that this growth of the epithelium is dependent

[1] Carrel, A., du Noüy, P. L., and Carrel, A., Cicatrization of wounds. IX, *J. Exp. Med.*, 1917, xxvi, 297.

on the state of the underlying connective tissue or granulation tissue as the case may be, it is yet most unlikely that the rate of epithelial growth indicates either the rate of the preceding repair of the subcutaneous tissues or its functional perfection. If conditions could be precisely defined it is probable that in the whole process of wound healing the period when the deep defect was being replaced by potential connective tissue would take its place as a latent period in the reaction of the epithelium.

We have found one account in the literature of an experiment made to measure the effectiveness of connective tissue repair. Sir James Paget[2] (1853) writes as follows:

"The strength, both of the new substance itself, and of its connection by intermingling with the original substance, is worthy of remark. To test it, I removed from a rabbit an Achilles tendon, which had been divided six days previously, and of which the retracted ends were connected by a bond of the size and texture usual at that period of the reparative process. I suspended from the half-section of this bond gradually increased weights. At length it bore a weight of ten pounds, but presently gave way with it: yet we may suppose the whole thickness of the bond would have borne twenty pounds. In another experiment, I tried the strength of a bond of connection which had been ten days forming: this, after bearing suspended weights of twenty, thirty, forty, and fifty pounds, was torn with fifty-six pounds. But surely the strength it showed was very wonderful, when we remember that it was no more than two lines in its chief diameter; and that it was wholly formed and organized in ten days, in the leg of a rabbit scarcely more than a pound in weight. With its tenacity it had acquired much of the inextensibility of the natural tendon. It was indeed stretched by the heavy weights suspended from it, yet so slightly that I think no exertion of which the rabbit was capable would have sufficed to extend it in any appreciable degree."

While these experiments were directed toward a study of the repair of tendons a superficial review of the conditions suffices to show that in the early days following tendon section it must be a value for connective tissue which is determined. This connective tissue may or may not be wholly representative, but it is difficult to devise a better experimental test for the reactive capacity of connective tissue. We therefore adopted the general method of Sir James Paget's experiments as a basis for further work. Our work falls naturally into

[2] Paget, J., Lectures on surgical pathology, London, 1853, i, 271.

two phases: (1) an effort to determine the rate of replacement of the tendon as measured by the strength of the connective tissue laid down between the cut ends; (2) an attempt to use the method in the study of the action of certain chemicals locally or generally applied and for the examination of that phase of the tuberculosis problem previously discussed.

Method.

Adult rabbits were anesthetized with ether. With various degrees of aseptic precaution the Achilles tendon was exposed and sectioned. At various intervals thereafter the animal was killed and the leg amputated at the hip and suspended by the knee through a strong wire loop as an intermediary to a stout chain hung from the ceiling. With a similar wire loop a pail was suspended from the hock. Into this pail clean sand was run from a funnel at a uniform rate and from a uniform height. When a break occurred the flow of sand was stopped, the pail, its contained sand, and all the apparatus coming away with the foot were weighed, the result being recorded in grams as the tensile strength of the newly formed tissue.

At the time the leg was amputated the tendon was dissected free from the surrounding tissue and covered with gauze wet with salt solution. After the leg was hung up, as a last step before the sand was run in, the tibia and the remaining soft parts were cut through with bone forceps and scissors. In this way the new tissue was protected against any irregular strain during the time of preparation.

In general the method can be said to have served its purpose. The difficulties and irregularities for the most part seem to be connected with the surgical procedure. Infection must be avoided as the presence of small pockets of pus in the connective tissue naturally weakens it. Hemorrhage at the time the tendon is cut cannot always be controlled and when the test is made the instances in which evidence of hemorrhage persists must be excluded. The tendon sheath must be carefully sutured at the time of operation. If this is not done the exudate extends through the opening and infiltrates the surrounding fascia. This then organizes and forms adhesions which may involve all the structures from the newly formed matrix of the tendon outward to the skin. On dissection it then is impossible to

isolate the representative tissue. The new connective tissue seems to spring from the old tendon sheath as well as from the cut ends of the tendon, or at least adhesions to the old tendon sheath are universal. If when the dissection is done an attempt is made to remove the last traces of old connective tissue, splits and shreds will be run down into the new tissue which would naturally weaken it. With care, however, the old tissue can be reduced to a thin film without damage to the new. It is not difficult to avoid the gross sources of error, and the variations due to minor faults probably do not affect the results in the main.

Experiments Bearing on the Healing of Wounds.

In the first sets of experiments, those intended to determine the general feasibility of the method, surgical cleanliness was sought through the use of antiseptic solutions. A coal-tar disinfectant of the creolin type was used in solution of appropriate strength for cleansing the skin, keeping the hair wet, and cleansing the hands and instruments. Ordinarily care was taken to touch the field of operation with instruments only and these were freed from excess of antiseptic. Protocols selected as being representative are summarized in Tables I and II.

The experiments recorded in Tables I and II were, as stated above, carried out depending upon an antiseptic solution for surgical cleanliness. In Table III is shown the result of an experiment in which the operative work was done with rigid aseptic precautions. All material used was previously sterilized in the autoclave. Gloves were worn and at the same time especial precautions were taken to keep dust and bits of hair from the skin of the animals from contaminating the wound. In this experiment dichloramine-T is again introduced.

It is not our present purpose to discuss the results of the three experiments presented so far with any pretense to finality.

The results of the second series are in accord with the expectation we entertained when benzene was administered to part of the rabbits. Benzene is known to cause an extensive aplasia of the lymphoid tissue and to give rise to an extreme leucopenia. It was expected to influ-

ence in a deleterious way the exudation processes involved in the repair or replacement of the tendon. The experiment, if its results are accepted at their face value, and we see no reason why they should not be so accepted, indicates that the method is adequate in that it is capable of revealing the action of extraneous influences brought to bear on the reparative process through systemic channels.

It will be noted that there is a large difference between the average tensile strength found in Tables II and III and that that in

TABLE I.

The Achilles tendons of rabbits were cut by open operation under ether anesthesia. The tendon sheath and skin were sutured separately. In the dichloramine-T series 7½ per cent dichloramine-T dissolved in chlorinated eucalyptol, specific gravity 1.2, was put into the tendon sheath and the remainder of the wound at the operation. A small amount remained when the sutures were tied. Breaking strength determined 10 days after section of tendons.

Untreated.	Dichloramine-T.
gm.	*gm.*
4,120	5,470
6,320	7,170*
6,620	7,520
7,750	9,100
7,900	9,370
8,050	10,520
10,070	12,200
10,600	
Average..... 7,678	8,764

* In this case the connective tissue did not break. The tendon pulled out of the muscle and the recorded strength is considerably too low.

Table I is intermediate to these. The low place of Table II is in part to be explained by the fact that when the first of the series were tested the operator made more effort to trim away all traces of the original connective tissue than has seemed practicable. In order that the experiment might not be lost the method was persisted in even though it seemed somewhat faulty. It is probably true also that there was in this series in general more evidence of slight persistent hemorrhage and low grade infection than in the others. The internal varia-

TABLE II.

Operation as in Table I. The rabbits in the benzene series had 5 cc. of 50 per cent benzene in olive oil administered subcutaneously on the day after operation. Breaking strength determined 7 and 10 days after operation.*

Untreated.		Benzene.	
7 days.	10 days.	7 days.	10 days.
gm.	*gm.*	*gm.*	*gm.*
2,270	3,900	1,900	
2,920	4,140	2,380	
3,120	4,400	2,430	
3,450	5,050	2,540	2,240
3,650	5,350	2,650	2,540
3,850	5,700	2,720	3,350
3,950	5,970	2,950	3,390
4,200	6,120	3,420	3,970
4,950	6,200	4,170	5,750
5,620	6,650	4,270	6,200
Average.3,798	5,348	2,943	3,917

* This whole experiment was carried out by Mr. R. H. Kennicott, then a special student in the Medical School of the University of Pennsylvania.

TABLE III.

Operation aseptic; otherwise as in Table I. In the dichloramine-T series the statements made in Table I about similar series also apply. Breaking strength determined at 10 days.

Untreated.	Dichloramine-T.
gm.	*gm.*
4,920	4,350
6,450	5,350
7,150	6,650
7,700	7,300
8,170	7,600
9,150	7,650
10,000	7,850
11,170	8,800
12,750	10,000
13,750	12,800
Average..... 9,121	7,835

tion in Table II is, however, no greater than the others, if it is as great.

The increased strength attained in 10 days in Table III contrasted with Table I is, we believe, accounted for by the improvement in operative technique—a careful aseptic method having been substituted for a rather crude procedure in which reliance was placed in an antiseptic solution. The fourth experiment (to be presented later), also done aseptically and after more experience, shows a still further increase in the average tensile strength.

In contrasting these experiments emphasis has been laid on the averages. A scrutiny of the tables shows that the averages are surprisingly representative. Where the average is higher it is not due to the presence of exceptionally high figures for individuals.

The dichloramine-T results are not such as to permit satisfactory interpretation. They might be taken to indicate that this material helped in the case of an imperfectly carried out antisepsis and hindered healing when asepsis was better. This substance is, in any event, not one which would be recommended to be left in wounds which are closed tightly as it is capable of causing an aseptic inflammation in the solvent used. Our purpose in including these figures at present is to make available all our data.

As a general method for the quantitative study of a fundamental aspect of wound healing we cannot feel that we have contributed anything in finished form. The wide variation in values found necessitates work on a statistical basis and if there prove to be no other limitation the method is obviously laborious.

Experiment on Tuberculosis.

Having in mind the possible place of the reactivity of the connective tissue in relation to the healing of tuberculosis as presented in the introductory paragraphs of this paper, we sought information by the application of the method as developed to the problem along the following lines. The fact that the length of life of animals of a given species inoculated with anything less than an overwhelming dose of virulent tubercle bacilli varies widely has recently been emphasized by the work of our laboratory. Whatever the reason may be the

strength of the newly formed connective tissue as determined above also varies over a wide range. We sought to determine whether the variations in the two cases were parallel or otherwise. With this purpose in mind the following experiment was carried out.

Young well grown rabbits, weighing about 1,500 gm., were chosen. The Achilles tendon of one leg was sectioned. On the 10th day the leg was amputated at the hip and the tensile strength of the reparative tissue was tested as described. The amputation was carefully conducted under ether anesthesia. Time additional to that needed

TABLE IV.

The rabbits weighed approximately 1,500 gm. The tendons were cut between October 1 and November 15, 1917, under ether anesthesia. Leg amputated and tensile strength of connective tissue determined on the 10th day. March 1, 1918. Inoculated all surviving animals with 0.02 mg. of tuberculosis culture, Bov. C., intravenously.

Length of life after inoculation of tubercle bacilli.	Tensile strength.	Length of life after inoculation of tubercle bacilli.	Tensile strength.
days	*gm.*	*days*	*gm.*
43	8,220	62	10,500
45	6,420	62	8,200
45	12,500	62	6,850
45	9,600	85	7,550
48	12,600	88	14,000
51	11,400	92	13,100
52	11,550	92	14,700
55	8,300	92	8,800
57	9,070	113	11,200
58	13,100	113	9,900
Average strength of first half to die.....	10,276	Average strength of second half to die.....	10,480

for healing of the operation wound was allowed for the perfect recovery of the animal from the effects of this precedure. The animals were then inoculated intravenously with a suspension of virulent tubercle bacilli (0.02 mg. of the growth on glycerol agar). Every effort was made to attain uniformity in this inoculation. The animals were then retained until they succumbed to the tuberculosis. In Table IV the length of life of the rabbits in days after the inoculation with tubercle bacilli is set over against the tensile strength of the

connective tissue in grams. Calculation shows that the average tensile strength of the connective tissue formed by the first ten rabbits to die is practically identical with that formed by the last ten animals.

It is apparent that no correlation appears, that consequently we have by this experiment demonstrated no relation between the reactivity of connective tissue in a normal reparative process and the general resistance of the animal to experimental infection with *Bacillus tuberculosis*. In fact the experiment seems sufficiently decisive to warrant the tentative conclusion that no relation exists between any dominant factor in the laying down of connective tissue in response to traumatism and natural resistance to tuberculosis.

SUMMARY.

1. A method has been revived which enables the connective tissue factor in wound healing to be studied quantitatively.

2. It has been found that the functional value of connective tissue formed in response to traumatism as represented by its tensile strength varies widely in different animals.

3. It is suggested that the method may find application in the study of extraneous influences which may affect wound healing either through local or systemic application.

4. It has been determined that there is no parallelism between an active connective tissue response to traumatism and natural resistance to inoculation tuberculosis in the rabbit.

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THE COMPLEMENT FIXATION REACTION AS APPLIED TO TUBERCULOSIS

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The purpose of this paper is to present certain selected observations bearing on the nature of the complement fixation reaction as applied to tuberculosis and also a summary of the study of a number of human serums. From neither point of view are the observations intended to be the basis of altogether final opinions. It is hoped that the results on the technical aspects of the reaction may be of service at this time to others who are using the method.

The literature of complement deviation in tuberculosis has been the subject of entirely adequate review by several recent authors, particularly Corper (1) and Von Wedel (2). I shall therefore omit all general references. This omission is further justifiable because such merit as this paper may possess rests upon an effort to make the results significant in a quantitative sense. So far as I am aware previous authors have not attempted to do this.

The experiments and general observations here recorded were carried out before the appearance of the recent publications of Wilson (3) and Von Wedel bringing out, respectively, the variation of "fixability" of guinea pig complement with tuberculosis antigen-antibody combinations and the increased fixing power of serum a week or more old as contrasted with fresh serum. Knowledge of these matters would, I believe, have made it easier to attain consistent results during the course of this work but probably would not have essentially altered the results obtained.

The work of competent European observers a decade ago had made it appear improbable that the complement deviation method could be used as a practicable aid to the diagnosis or prognosis of tuberculosis. The question has recently been reopened by a number of American observers, most of whom assign at least a limited usefulness to the

method, while some are enthusiastic as to its value. Comparing the work of the two periods in a very general way there are differences in the methods employed which may conceivably account for the differences in results.

The workers both of the earlier period and more recently are for the most part agreed that complement deviation can often be elicited with the serum of infected animals or tuberculous people by using the tubercle bacillus or products of its growth as antigen in the reaction. It has been tacitly assumed by most workers that such reactions as are obtained are an evidence of the existence of specific antibodies in the serum. Noguchi (4), however, after a careful survey of the field came to the belief that the deviations obtained were not really specific, tuberculous sera reacting in his opinion quite generally although irregularly with peptones or other protein degradation products.

Over a year ago Dr. J. F. Bredick took up studies both of and with the method in our laboratory. His work involved the examination of the deviating properties of the serum of a number of the ambulatory patients coming to the dispensary of the Phipps Institute. He followed as closely as possible the methods of certain of the then more recent workers in the field, particularly in the matter of the antigen used, the quantities of reagent employed, and the time relations observed. His results are to be found in table 1 which also includes for the sake of comparison and summary the reported results of some other recent observers.

Bredick's results in general are seen to be lower in percentage of positives than those of Petroff and Bronfenbrenner, and higher than those of Corper, as based on the double plus criterion which this author puts forward as most significant. Bredick used as antigen either saline suspension of living tubercle bacilli (2 mgm. per cubic centimeter) or the same suspension which had been in the incubator under toluol from a number of days to several weeks. Otherwise he followed the plan of work which he had learned from Petroff some months before; that is, he used the rabbit antisheep hemolytic system and two units of guinea pig complement and two units of amboceptor. Some allowance was made for the natural antisheep amboceptor in the test serum by an intermediate incubation period of fifteen minutes after the addition of sheep corpuscle, amboceptor being added only to those pairs of tubes in which the serum control showed incomplete or no hemolysis at this time. The results were recorded at the fifteen minute

period of the second incubation. Any inhibition showing at this time was recorded as positive reaction.

What I saw of Bredick's work in progress and a comparison of his results with those of others suggested that a much more critical consideration of the technical aspects of the subject than was to be found in the literature was necessary before it would be worth while even to attempt to harmonize our results with those of other workers, either those who had obtained more or those who had found less positive reactions. In the face of many interruptions forced by extraneous circumstances I have tried to follow to a conclusion some aspects of the subject. This has involved the patient coöperation of the clinical staff of the institute in the collection of serum and the study of cases. I am

TABLE 1

OBSERVER	CLINICALLY ACTIVE		QUIESCENT		CLINICALLY NORMAL		SUSPECTED		OTHER DISEASES	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Bredick, 1917	19	3	19	59	1	9				
Petroff (5), 1917	199	13	89	69	3	75	65	101	6	35
Corper (1), 1916, (++) Bac. Em.	106	154	14	53	2	23	5	6		
Corper (1), 1916, (+) Bac. Em.	156	104	26	41	6	19	6	5		
Bronfenbrenner (6), 1914, non-syphilitic (W-neg.)	61	4	15	12			36	14	30	345

especially indebted to Dr. C. M. Montgomery for blood specimens and notes on the history and condition of over 200 individuals, collected for me during the past year. With this material the more fundamental of the following experiments were carried out.

REACTION TIME

It is somewhat surprising that those who have written on the subject of complement deviation in tuberculosis in recent years have so generally neglected to state completely the precise methods used in the test and especially in the recording of their results. Petroff (5) in his first paper gives a very careful description of his reagents and the quantities employed but does not state the time at which results are recorded nor does he give any hint as to what measure of significance he attaches to the lesser degrees of deviation which are of course frequently encountered. It is probably fair to infer that most of the

recent work has been done on the basis of reading the results in close comparison with the controls and recording deviations at about fifteen minutes after completing the hemolytic system. The older authors following the accepted Wassermann system presumably paid little attention to the transient deviations and this doubtless accounts for many of the differences in results recorded in the respective periods.

There is, of course, no *a priori* reason why the system recently followed should not be considered. But as one proceeds to put it into practice it is found to offer difficulties of interpretation which are nearly insurmountable. These difficulties seem to me to be inherent. At fifteen minutes after the hemolytic system is completed the whole reaction is in a state of flux. In the hemolytic system considered alone, it is true that with two units complement and two units amboceptor hemolysis is always complete in this time. In a complete titration of complement and amboceptor, however, the reaction with the lower concentrations of reagent are by no means complete in fifteen minutes. If the tubes are incubated in the water bath the single unit quantities are only precisely defined in one half-hour and the partial reactions are not stabilized even at that time. At fifteen minutes the state of the reaction is likewise still under the influence of the temperature of the reagents added and of minor faults of measurement which are difficult to avoid in practice.

Moreover, in carrying out a complete test there are added to the pure hemolytic system at least three factors of uncertainty aside from the specific deviation which is the object of the study. Serum and antigen are inherently inhibitory and more precise studies which I shall record later show that in the quantities used these reagents have action, even though this is masked in the presence of two units complement and two units amboceptor, and, moreover, that this action is of an irregular nature, probably dependent on variations in the complement and cannot be precisely controlled. The human serum contains also an extremely variable amount of antisheep amboceptor and this can at best be only roughly controlled. As a practical consequence of these factors it is really very difficult to obtain readings at the end of fifteen minutes which check with accuracy on repetition. While all recent authors have advanced the belief that the antigen employed is the factor accounting for the differences in result obtained it is my belief that the various readings of the result of the reaction in this period when it is necessarily incomplete are fully as responsible as any other factor for

the lack of a reasonably precise agreement. The recent publication of Corper and Sweany (7) is quite in accord with this view.

However this may be, it is a fact that complement deviation with the serum of most tuberculous persons, with any of the antigens I have so far employed, is usually a transient phenomenon when determined at fifteen minutes after completing the hemolytic system, the primary incubation being one hour or two hours. At thirty minutes secondary incubation the reaction is nearly complete. But the percentage of positives which could be recorded at thirty minutes would be very low. The serum which will give a permanent four plus reaction under these conditions is exceptional in my experience.

On consideration it seemed quite possible that, assuming these transient reactions to be instances of specific deviation, the method employed might be faulty in that the deviation reaction was tested before the union (antibody—antigen—complement) had become complete. Some experiments to see if union could be hastened by raising the temperature during the primary incubation failed of result, possibly because of the small latitude open to trial in view of the thermolability of the complement. Attention was then turned to the reaction time. The conclusion is evident from the following protocols which give the results of an experiment designed to bring out the influence of the factor of fixation time on the degree and durability of the fixation.

In general the system I have used is the combination rabbit anti-sheep amboceptor, guinea pig complement (1+9 dilution). Volume 1.5 cc for the first incubation is raised to 3 cc. for the second period. The sheep corpuscles were used in 5 per cent suspension, 0.5 cc. per tube. All records are in terms of hemolysis (++++ indicating complete solution), except when in a few instances the results of the syphilitic deviation are included, when these are recorded in the opposite way as is now customary. All human sera were inactivated before use.

The reagents were first carefully titrated (table 2 A).

Five human sera which had been previously tested and found likely to give reactions varying from negative to strong positive were selected, reheated to 56°C. for one half-hour and used in 0.1 cc. quantity in the following test (table 2 B).

It was to be expected that in six hours incubation the reagents of the hemolytic system might have suffered. Accordingly the following control test was carried with the above series (table 2 C).

This experiment made it clear that an increase of the fixation period (primary incubation) intensifies the reaction and renders it more permanent. The test of the hemolytic system shows that its activity is somewhat lessened by six hours' exposure of the amboceptor complement mixture to a temperature of 37° to 38°C. It is also evident that each serum tested showed some deviation in the later hours of the test and that a slight anticomplementary action of the antigen appears for the first time at the sixth hour.

At the time these appearances were ascribed to the loss of complementary strength and it was reasoned that six hours was a longer exposure than the properties of the reagents would permit to be used.

TABLE 2A

August 19, 1917. Complement and amboceptor dilution prepared August 18, retitrated as follows: Anti-sheep amboceptor, 0.5 cc. — 5 per cent corpuscles, total volume 3 cc.

COMPLEMENT (1 + 9)	AMBOCEPTOR (1–1000)	5 MINUTES	10 MINUTES	15 MINUTES	20 MINUTES	30 MINUTES
0.5	0.5	+	++++	++++	++++	++++
0.5	0.4	0	++++	++++	++++	++++
0.5	0.3	0	+	++++	++++	++++
0.5	0.2	0	0	+++	++++	++++
0.5	0.1	0	0	0	0	+
0.5	1.0	++++	++++	++++	++++	++++
0.4	1.0	++++	++++	++++	++++	++++
0.3	1.0	0	++++	++++	++++	++++
0.2	1.0	0	+	+	++	++
0.1	1.0	0	0	0	0	0

Result: 0.2 cc. amboceptor dilution = 1 unit.
0.3 cc. complement dilution = 1 unit.

Further experiment showed clearly that if complement was used on the day of its collection this loss of activity was not demonstrable. In six hours most sera still showed deviating qualities. Some experiments were tried with the ice box fixation method which came to nothing. Fixation was good if the mixture was incubated for an hour on the second day but not if this incubation was omitted. This incubation on the second day seemed, however, to be very harmful to the reagents, which acted most irregularly thereafter. I therefore proceeded on the following plan for a time.

The fixation period of four hours was adopted as giving an appreciable advantage in the permanency of the reaction. Two units of com-

TABLE 2B

PRIMARY INCUBATION 1 HOUR			AMBOCEPTOR	CORPUSCLES	SECONDARY INCUBATION		
Complement (1 + 9)	Antigen	Serum Number			15 minutes	30 minutes	Over night
	cc.						
0.6	1	499	0.4	0.5	0	++	++++
0.6	1	507	0.4	0.5	++++	++++	++++
0.6	1	502	0.4	0.5	++++	++++	++++
0.6	1	500	0.4	0.5	++++	++++	++++
0.6	1	512	0.4	0.5	++++	++++	++++
0.6	1	—	0.4	0.5			
PRIMARY INCUBATION 3 HOURS							
0.6	1	499	0.4	0.5	0	0	0
0.6	1	507	0.4	0.5	0	++	++++
0.6	1	502	0.4	0.5	+++	++++	++++
0.6	1	500	0.4	0.5	+++	++++	++++
0.6	1	512	0.4	0.5	+++	++++	++++
0.6	1	—	0.4	0.5	++++	++++	++++
PRIMARY INCUBATION 4 HOURS							
0.6	1	499	0.4	0.5	0	0	0
0.6	1	507	0.4	0.5	0	+	++++
0.6	1	502	0.4	0.5	+	+++	++++
0.6	1	500	0.4	0.5	+	+++	++++
0.6	1	512	0.4	0.5	+	++	++++
0.6	1	—	0.4	0.5	++++	++++	++++
PRIMARY INCUBATION 5 HOURS							
0.6	1	499	0.4	0.5	0	0	0
0.6	1	507	0.4	0.5	0	0	+
0.6	1	502	0.4	0.5	0	+	++++
0.6	1	500	0.4	0.5	0	+++	++++
0.6	1	512	0.4	0.5	0	++	++++
0.6	1	—	0.4	0.5	++++	++++	++++
PRIMARY INCUBATION 6 HOURS							
0.6	1	499	0.4	0.5	0	0	0
0.6	1	507	0.4	0.5	0	0	+
0.6	1	502	0.4	0.5	0	+	++++
0.6	1	500	0.4	0.5	0	+	++++
0.6	1	512	0.4	0.5	0	+	++++
0.6	1	—	0.4	0.5	+++	++++	++++

plement and two units of amboceptor were used. The reaction was read after a secondary incubation of one-half hour and a subsequent stay in the ice box over night. About one hundred sera were studied on this basis. The result was no more satisfactory than before. Definitely tuberculous cases failed to react. Sometimes whole series showed positives when there seem no apparent reason for it in the quality of the reagents. Reactions with the same serum on consecutive days frequently failed to agree. The only certain result, and this I thought important, was that a certain considerable number of sera gave *permanent* four plus reactions under this system.

TABLE 2c

INCUBATED 6 HOURS		SECOND INCUBATION				
Complement (1 + 9)	Amboceptor (1–1000)	5 minutes	10 minutes	15 minutes	20 minutes	30 minutes
0.5	0.5	0	++++	++++	++++	++++
0.5	0.4	0	+++	++++	++++	++++
0.5	0.3	0	+	++	+++	++++
0.5	0.2	0	0	+	++	+++
0.5	0.1	0	0	0	+	+
0.5	1.0	+++	++++	++++	++++	++++
0.4	1.0	0	+++	++++	++++	++++
0.3	1.0	0	+	+++	++++	++++
0.2	1.0	0	0	0	0	0
0.5	1.0	0	0	0	0	0

0.3 cc. amboceptor dilution = 1 unit.
0.3 cc. complement dilution = 1 unit.

MEASURE OF COMPLEMENT COMPLETELY BOUND

A consideration of the preceding results made it appear that complement deviation with tuberculosis reagents manifested itself with less vigor than in the case of syphilis, and it seemed important to determine whether even in the case of the stronger sera acting for four hours the reaction were really complete and permanent or whether on the contrary it might not be reversible. Reversibility of reaction if demonstrated would, of course, have been an understandable explanation of the irregularities encountered.

Test of this point was to be made by adding the hemolytic amboceptor in clear excess. Experiments for this purpose were from the beginning made with varying quantities of complement. It developed under

these conditions that the reaction is a comparatively complete and stable one. The exact limitations as to reversibility were not finally developed, the experiments indicating that it was of minor importance and giving at the same time indications of what seemed to be a manageable method possessing precise advantages. The point of advance was that the use of a long primary incubation time, graduated amounts of complement and an excess of hemolytic amboceptor, gave a result which minor variations in conditions or technique could not easily disturb, a test carrying an important measure of intrinsic control. The addition of an excess of hemolytic amboceptor also disposed of the natural antisheep amboceptor as a factor in the reaction. In practice ten units of amboceptor were found to be a clear excess and approximately this quanity was employed. An increase to twenty units is not objectionable except as a waste. If thirty units are introduced there is occasionally an interference with hemolysis, possibly an evidence of the operation of the "*ablenkung*" phenomenon of Neisser and Wechsberg.

The scheme followed is illustrated by the following experiment which shows again the influence of fixation time on the result. This particular serum is not especially strong although it gives a clear cut positive reaction in my present judgment. The experiment does not develop the permanency of the reaction. If these tubes had been further kept in the ice box over night any differences between the one hour tubes and the controls would have disappeared. In the four hour tubes the hemolysis would, in accordance with much other experience, have increased by a single plus sign more or less uniformly down to and including the 0.4 cc. of complement (see table 3).

The method in the form illustrated by the preceding experiment 3 seemed worthy of careful trial and with it I returned to the study of a series of blood serums from tuberculous cases. Table 4 is the protocol of one day's observation on this plan.

In attempting to interpret the following protocol, Table 4, it is to be noted that the antigen alone in the amount used had no demonstrable anticomplementary value (line 2 compared with line 1). The serums alone have a variable anticomplementary value (second line in each case compared with line 1). Taking the amount of complement, read from right to left, at which hemolysis is first complete (++++), and subtracting 0.2 cc. as the similar value for complement alone the anticomplementary values are G. = 1, Pa. = 0, Le. = 1, Mc. = 1, Br. = 0, and He. = 1.

This result is fairly typical of the general run of human serums. Translating the terms of this experiment into the form more usual we see that with complement alone 0.2 cc. gives complete hemolysis and, as the amboceptor is here used in excess, this is also what is, in the general accepted terminology, one unit of complement. Four-tenths cc. then is two units and this is the quantity usually employed when observations are made at a single point. It is to be noted that four of the six sera used have inherent inhibitory qualities which leaves only 0.1 cc. of complement or $\frac{1}{2}$ unit as a margin for the determination of any specific deviation. It is rare for the

TABLE 3

Time relations of deviation reaction and amount of complement bound

TIME OF FIRST INCUBATION	AMOUNT OF COMPLEMENT (1 + 9 DILUTION)						
	1 cc.	0.8 cc.	0.6 cc.	0.4 cc.	0.3 cc.	0.2 cc.	0.1 cc.
1 hour	++++	++++	++++	+++	+	0	0
2 hours	++++	++++	++++	+	0	0	0
3 hours	++++	++++	+++	0	0	0	0
4 hours	++++	++	+	0	0	0	0
Controls:							
Antigen + Complement 4 hours				++++	+++	0	0
Serum + Complement 4 hours					++++	++	0
Complement only 4 hours					++++	+++	0

The constants in this experiment are 0.1 cc. human serum; 0.05 cc. antigen number 4, alcohol soluble fraction; and an excess of antisheep amboceptor (10 units). The second incubation was one-half hour. Readings at once.

antigen alone to show a total lack of anticomplementary value in the quantities recommended for use and any summation of these two non-specific inhibitory factors with but two units of complement tends to produce partial positives in the next tube of the series. In view of this quantitative relationship and the narrow margin it is not surprising that the results from day to day with the same serum and antigen are frequently inconsistent when two units of complement alone are made as the basis for judgment.

In the test we are discussing it is to be seen that the specific inhibition (serum + A) varies greatly, (complete at 1 cc. with serum G. to none whatever with serum He., when measured by

the amount of complement giving complete hemolysis). These cases are all advanced cases of tuberculosis. The patient G. died a few weeks after this test was made. It is evident that the amount of deviation as measured by the amount of complement bound varies in undoubted cases of tuberculosis within wide limits, being practically nil in some cases. The prevaling view that the cases of this

TABLE 4

April 3, 1918. T. B. deviation. Advanced cases Jefferson Hospital

CONSTITUENTS OF TEST	AMOUNT OF COMPLEMENT (1 + 9 DILUTED)							FIXATION VALUE
	1 cc.	0.8 cc	0.6 cc.	0.4 cc.	0.3 cc.	0.2 cc.	0.1 cc.	
Complement only.....	—	—	—	—	—	++++	+++	
Complement + antigen.....	—	—	—	—	—	++++	+++	
Serum G + Antigen..	0	0	0	0	0	0	0	
Serum G only.....	—	—	—	—	+++*	++	+	7+
Serum Pa. + Antigen.	—	++++	+++*	+	0	0	0	
Serum Pa. only.....	—	—	—	—	—	++++	+++	6
Serum Le. + Antigen.	++++	+++	++	*	0	0	0	
Serum Le. only.....	—	—	—	—	++++	+	0	7
Serum Mc. + Antigen.	—	—	—	++++	+++	++	0	
Serum Mc. only.....	—	—	—	—	++++	+++	+	1
Serum Br. + Antigen.	—	—	++++	++	+	*	*	
Serum Br. only.....	—	—	—	—	—	++++	+++	4
Serum He. + Antigen.	—	—	—	—	++++	*	0	
Serum He. only.....	—	—	—	—	++++	+++	+	0

Primary incubation four hours.
Excess of amboceptor added.
Second incubation one half hour.
Reading over night.
Antigen used 0.1 cc. Petroff glycerin extract (diluted 1 + 19).

type failing to react are the exhausted and dying cannot at present be regarded as at all accurate.

It is to be noted also as shown in the last column of the table that a numerical expression can be given to the result of the reaction by subtracting the amount of complement inhibited by serum alone from that inhibited by serum + antigen. This value I have spoken of as the fixation value of the serum.

In all 145 serums were titrated for the amount of complement they could permanently bind. The antigen employed was a heavy suspension of a single human type culture kept in the incubator under toluol. The use of this preparation was not begun until it was several weeks old. It therefore was in its nature a mixture of autolytic products (according to Corper) and the bacillary residue. The toluol had partially extracted the fatty matter although it is very unlikely that this extraction was complete. The preparation was shaken each time on the day before the removal of the material for that day's work. This removal was accomplished with a pipette inserted well below the toluol layer.

Table 5 gives the results of the study of these 145 serums arranged to show the relation between the fixation value found and the type of case furnishing the serum.

TABLE 5

TYPE OF CASE	NUMBER OF CASES ACCORDING TO FIXATION VALUE									
	0	1	2	3	4	5	6	7 and over	4 or more in per cent	3 or less in per cent
Non-tuberculous	7	10	3	6	1	1	0	2	$13\frac{1}{3}$	$86\frac{2}{3}$
Incipient quiescent	1	3	2	1	1	1	1	0	$33\frac{2}{3}$	$66\frac{2}{3}$
Incipient active	0	0	0	0	1	0	0	2	100	0
Moderately Advanced quiescent	2	1	0	1	0	0	1	3	50	50
Moderately Advanced active	0	0	0	0	2	0	0	3	100	0
Far Advanced inactive	0	1	0	0	1	1	1	1	80	20
Far Advanced active	0	8	2	2	9	2	6	12	70.7	29.3
Tuberculosis certain, classification irregular	0	1	0	1	5	1	0	5	84.6	15.4
Diagnosis uncertain. Tuberculosis possible but not demonstrated	0	5	4	0	3	3	4	5	62.5	37.5

If table 5 is examined with the purpose of selecting a single fixation value which shall be decisive in the diagonsis of tuberculosis this is at once seen to be impossible. With almost any type of case fixation values are to be found on either side of any vertical drawn on the chart. If the non-tuberculous cases are considered it is seen that the numbers having fixation values of 4 or more are appreciably fewer than those having the value 3 or less than 3.

Assuming for the moment that the dividing line between fixation values 3 and 4 may have critical value it has been drawn through the chart and the percentages in each class lying above and below this line have been calculated and added to the chart. If the attempt is made to assign critical significance for the diagnosis of tuberculosis

to any fixation value here appearing it will be seen that no more favorable line can be drawn than that between 3 and 4. If one goes lower a great loss occurs among the non-tuberculous. If one goes higher a very considerable loss occurs among the various tuberculous classes. It is evident that this method is not able to discriminate precisely between the tuberculous and the non-tuberculous. The best that can be done is to say that a pronounced reaction is to be obtained in a considerable number of cases in which there is no other evidence of the existence of tubercle ($13\frac{1}{3}$ per cent in this series); and that an even higher proportion fail to react even though they are to be regarded as definitely tuberculous. Omitting the incipient quiescent group for the sake of argument, as being subject to errors of clinical judgment in a considerable degree, the average among the other tuberculous groups which deviate with a value of 3 or less is 19.1 per cent.

TITRATION AGAINST THE ANTIGEN

An interval of several months now occurred in which my clinical associates and I were involved in other work and nothing could be done to develop this subject. Resuming I began with antigens kindly furnished me by Mr. Petroff and with sera obtained partly from our clinic and partly from the Jefferson Hospital, (Branch for Diseases of the Chest), through the activity of Dr. H. S. Newcomer. For access to the Jefferson Hospital material I am much indebted to Dr. E. H. Funk. It was evident at once that with these antigens a large number of cases of tuberculosis were giving threshold reactions or none. Yet certain sera reacted strongly enough to make it plain that the antigens were not a fault. I therefore approached the matter again from a somewhat different angle.

Keeping the four hour fixation period and still using the excess amboceptor, I used a fixed amount of complement,(0.5 cc. which is nearly always $2\frac{1}{2}$ units), with a variable amount of antigen. Table 6 illustrates this proceedure.

Inspection of Table 6 shows that, with the exception of serum number 4, each one tested at that time shows deviation of complement (or perhaps better, inhibition of complementary action), when contrasted with the "antigen only" control at the bottom of the table. Some give more deviation than others. Serums numbers 2, 3, 7, 8, 9, 15 and 18 I have marked with X in the last column of the table and these may be considered to be of intermediate or average deviating powers.

TABLE 6

Complement deviation. Enlisted men, United States Navy

Wassermann with cholesterinized antigen. T. B.: upper line, Petroff glycerine extract (1 + 19 dilution); lower line, salt solution suspension, culture J. G., 10 mgm. per cubic centimeter. Four hour primary incubation. Ten units amboceptor. Thirty minutes secondary incubation. W = Wassermann record in terms of deviation. T. B. record in terms of hemolysis.

SERUM NUMBER	WASSERMANN	T. B. ANTIGEN AMOUNTS				SUMMARY
		0.4 cc.	0.3 cc.	0.2 cc.	0.1 cc.	
1	—	0	0	+	++++	
		—	+	+	++++	+
2	++++	+	++	++++	++++	
		+	+	++++	++++	x
3	++++	+	++	++++	++++	
		+	+	++	++++	x
4	0	++++	++++	++++	++++	
		+++	+++	++++	++++	—
5	0	0	+	+++	++++	
		0	0	++	+	+
6	++	0	0	*	++++	
		0	0	0	++	+
7	0	+	++	++++	++++	
		+	++	++++	++++	x
8	++++	+	++	++++	++++	
		+	++	++++	++++	x
9	0	+	++	+++	++++	
		+	++	++++	++++	
10	0	0	+	+++	++++	
		0	+	++	++++	x+
11	0	0	0	++	++++	
		0	+	++	+++	x+
12	0	0	+	++	++++	
		0	0	+++	++++	x+

TABLE 6—*Concluded*

SERUM NUMBER	WASSERMANN	T. B. ANTIGEN AMOUNTS				SUMMARY
		0.4 cc.	0.3 cc.	0.2 cc.	0.1 cc.	
13	0	0 0	0 0	0 +	+++ ++*	+
14	0	0 0	+ +	+++ ++	++++ ++++	x+
15	0	++ 0	++++ +	++++ +++	++++ ++++	x
16	0	+++ +++	++++ +++	++++ +++	++++ ++++	—
17	0	+ 0	+++ 0	++++ 0	++++ 0	+
18	0	+ +	+++ ++	++++ +++	++++ +++	x
Antigen only...	—	+++* +	++++ +++*	++++ ++++	++++ ++++	

Serums numbers 4 and 16 marked — have less activity than these. Serums numbers 10, 11, 12 and 14 marked X+ have slightly more power than the average. Serums numbers 1, 5, 6, 13 and 17 marked + have considerably more inhibitory activity than the others. On this system, using several antigens, often several with the same sera, I have examined serum from 247 individuals. The above table is truly representative of the situation. It is not usually possible to separate the groups very precisely but one has no difficulty in picking out the cases which are an extreme in their departure from the usual or average reaction. Numbers 4 and 16, 6, 13 and 17 strike one at once as being clearly different from the majority.

Before trying to develop the significance of these results it should be noted that whenever in the column, 0.1 cc., there is less than complete hemolysis the reaction is one which would be generally regarded as a positive deviation in some degree according to the standards now current. In order to be conservative I have considered only those cases giving one plus or no hemolysis in this column as being of real interest.

The 247 individuals examined by this method have all been men on active service in the United States Navy. Many of them were suffering from venereal disease, most being either syphilitic or suspects. In no case has there been reason in the physical condition of the man to suspect that he was suffering from active tuberculosis. In fact, except for the necessity of quarantine in certain cases of florid syphilis, or the necessity of relief from duty for administration of salvarsan, there were few if any cases in the list who were not entirely fit for duty.

Among the 247 cases there were found 26 or 10. 5 per cent who gave distinctly more than the usual or average reaction. In eight cases classification was impossible. Three of these gave average reactions on one occasion and more than usual on another. The other five were intermediate between the usual and the definitely increased on the day this test was carried out. Off-setting the three cases which gave different reactions on different days there have been a number in which the reaction has been carried out repeatedly with the results in agreement. Some of these have been weak and some strong in their fixing form.

In order to make the comparison between this method of test and that previously described, four serums have at different times been tested for the quantities of complement they were capable of binding. These were selected as being very definitely stronger than the average human serum in deviating capacity when tested against antigen. They gave the figures 6 and 7 on the system previously described (test against complement). That is, they are definitely in the class of deviation found chiefly among the tuberculous.

With the courteous coöperation of the medical officers of the various commands to which the men were attached it was possible to review the history and present physical condition of a number of the twenty-six men giving strong reactions. The examinations were conducted by Passed Assistant Surgeon, F. J. Dever, U.S.N.R.F., to whom I am much indebted. Sixteen men were examined. None of them were ill in any way which suggested that they were suffering from tuberculosis. One individual had had two attacks of pleurisy. The brother of one, and the aunt and uncle of another had died of tuberculosis. X-ray examination showed prominent peribronchial glands in one of the men. Otherwise both physical examinations and history were completely negative. It is evident therefore that the deviation test in individuals free from demonstrable tuberculosis may

give rise to reactions which cannot be distinguished from those given by characteristically diseased persons.

In order to further develop the relation between the results of the two methods of titration which have been described I have carried out the examination of a few serums from tuberculous individuals using the antigen as the variable factor. The results is to show that even on this most delicate system a number of individuals fail to react more strongly than the average. The number of examinations so far done is small and the percentage could not be of value.

The results obtained by the two systems of titration are in fair accord. Considering the fact that they were carried out on entirely different individuals it may be said that they completely agree in showing that from the purely diagnostic point of view complement deviation fails to give significant reactions in about 20 per cent of proved cases of tuberculosis and that reactions at present indistinguishable from the moderately strong type among the definitely tuberculous are found in at least 10 per cent of young men in who there is no other evidence of tuberculosis.

It would seem therefore that as an aid to diagnosis the test as so far developed can have little value. It may be argued that the Wassermann test for syphilis—admittedly of enormous practical importance—also has a high percentage of deficiency in the chronic or latent stages of the disease. This objection does not really have point as in syphilis all of the error is in the failure of certain cases to react, and these cases may for the most part be subjected to relatively simple and inexpensive therapeutic measures which by their result are likely to throw further light on the nature of the case. The error due to false positives in the case of syphilis probably does not exceed one per cent, and if the results of the Wassermann test are carefully correlated with the clinical condition as determined in other ways the number of cases erroneously considered to be syphilitic would be much less than this low figure. The failure to react on the part of the proved tuberculous case is by no means confined to the extremely advanced group on the verge of dissolution. It does seem to be generally true and it is interesting, that the small number of cases classed as incipient active, and moderately advanced active, all gave definitely positive reactions (table 5). This may be taken as evidence that the reaction is really specific and that it may be characteristic of a type of tuber-

culosis in which the lesions are for the most part progressing, but have not yet proceeded to extremes.

As off-setting this opinion there stands out the fact of reactions on the part of apparently healthy individuals. How is this to be explained? It is true that at least 90 per cent of individuals give some deviation as measured against the anticomplementary value of the antigen. Some may be tempted to see in this a substantiating analogy emphasizing the significance which has been given to the almost universally positive Pirquet reaction on the part of adults. However, it may later be shown that these slight deviations are in large measure non-specific in Noguchi's sense. Those individuals (about 10 per cent) who show strongly positive reactions cannot be accounted for in this way unless it is to be admitted that the whole system is so complicated by the presence of non-specific reaction as to be worthless. It is perhaps not unlikely, in view of the fact of what we know of the presence of anatomical tubercle among persons coming to autopsy for other conditions, that these men really have a focus of disease, but one of such character as not to influence their general health.

In this connection it is necessary to consider the relation of this reaction to syphilis. Of those otherwise healthy individuals who gave deviations much stronger than the average, somewhat more than one-half gave positive Wassermann reactions with syphilitic antigens. It is also true that somewhat more than half of all the sera tested in the series gave positive Wassermann reactions so that there is no suggestion that the deviation reaction is non-specific in this sense. In two cases the deviation reaction with tuberculous antigens was found positive a week or two before the Wassermann reaction became positive. The facts suggest the possibility that the presence of syphilis and the vigorous treatment for this disease to which these men were subjected (both mercury and salvarsan in full doses) may activate small tuberculous lesions to the point where the deviation reaction develops. There is, however, in the series so far, very little evidence of even this departure from an explanation on the basis of pure coincidence.

Approaching the complement deviation reaction from a quantitative point of view I have so far then considered the factor of time, the amount of complement bound, and the influence of antigen concentration. The variations in the hemolytic system have been reduced to a minimum by the use of an excess of amboceptor. I have

not, up to the present time, tried the titration of the antibody content of the serum on any large scale. It is probable that from the diagnostic point of view this could be of little value as a matter of *decreasing the serum amounts*, and it may be predicted with some confidence in view of the results with variable quantities of antigen that *increasing* the amounts of serum would not change the result, at least until certain other factors of uncertainty are eliminated. Certain advantages have resulted from the adoption of these methods. Many troublesome questions still require consideration. The two vital factors in the reaction, the serum and the antigen, seem to fluctuate to a certain extent from day to day in their value. The complement is of course never twice the same. Much more precise studies are required in an effort to establish one or more standard antigens and to determine if possible the range of serum and complement fluctuation.

Certain European workers had attempted to standardize the reaction using a strong antituberculosis serum produced by the Hoechst Company as the basis for the work. This effort seems to have met with limited success at least, but not many data are available. I wish at this time to record some experiments which may by further development make possible increased precision or possible even standardization in the application of the complement deviation reaction to tuberculosis problems.

CHARACTERIZATION OF THE CONSTITUENTS OF THE REACTION

In my approach to the question of standardization I have used the serum as a starting point. For some time I made it a practice to add an equal part of glycerin to the remainder of many serum samples. These were pooled, roughly classified as strong, medium, weak, and negative, and kept in the ice box. The first efforts to use these mixed glycerinated serums were disappointing. In a couple of weeks after glycerination the serum is always strongly anticomplementary and I have found no way of removing this property. Heating to 56° no longer affects the inhibitory factors, at least to any practicable degree. Such efforts as I have made to remove the inhibition by extracting with ether, or by absorption with red cells (Noguchi's methods for protectin) have also failed. Fortunately with the passage of time the anticomplementary properties disappeared spontaneously. Serum glycerinated in July, August and September, 1917,

was worthless in October and November of that year, but gave good results again in March and April, 1918.

At this latter time I had quite a supply of strong serum prepared in this way. Those serums of the preceding summer which had been titrated against complement and found capable of binding completely 0.8 cc. of 1 + 9 dilution or more had been bottled together. This mixture was now tested with various antigens and found capable of binding approximately the same amount, namely, 1.0 cc. of the usual complement. I am unable to be precise, but have reason to believe that when originally put away the mixture might have been capable of binding between 1.2 cc. and 1.5 cc. of complement. Six months would have caused, if this were true, about 20 or 30 per cent loss of strength. The observation would indicate that with greater care it would easily be possible to establish a fairly stable serum standard in some such way as this. However this may eventuate, I had available a considerable supply of serum which was used over a period of three weeks to study the properties of some antigens and the results can be viewed with confidence so far as they go because the serum was certainly a practical constant during that period. A few of the results I report were extended by repetition with single freshly obtained serums. These probably have less universal value but as this part of the report must at present be considered as preliminary I shall make no distinction between the two types of observation in drawing tentative conclusions. The experiments concern chiefly the properties of various antigen preparations.

The older European observers most often used old tuberculin as an antigen when trying to apply the complement deviation method to the study of tuberculosis. In various abortive attempts to apply the method of a number of years ago I met with failure, which, in view of the time relationships I have above described, I am inclined to attribute to having at that time followed the Wassermann technique too literally. Recently I have reëxamined this matter, using the strongly reacting pooled serum above described as the source of antibody. The antigens have been various filtrates and concentrates of old bouillon cultures of the tubercle and bacillus suspensions of the tubercle bacillus variously treated. Some preparations were made according to the exact method used in the production of old tuberculin, others were simple bouillon filtrates, and still others were intermediates, in

that they were concentrated at low temperature. No determination of tuberculin strength was made.

As a rule no antigenic value could be immediately demonstrated in those bouillon preparations which had been heated. When present the difference between the anticomplementary and antigenic values was slight. I then sought to purify the tuberculin according to the accepted methods by alcohol precipitation. The precipitates when redissolved gave about the same result as the original preparations. The differences between anticomplementary and antigenic values were less if anything than in the originals. Without expecting any result I then examined the filtrates and to my surprise found them active as antigens.

Without going into the details of the experiment it may be said that with any sample of bouillon filtrate or any concentrate of the same which I have had for examination and with all of the glycerin extracts of the bacillary bodies which I have made or received from others, the anticomplementary properties are partly removed by precipitation with alcohol (80 volumes per cent). When the filtrates are evaporated to restore the original volume it is found that they contain antigen and that this is often approximately that originally present, the anticomplementary properties being much reduced.

An interesting question which has been in part answered by these immediately preceding observations concerns the thermal relationships of the antigen and it is evident from the results recorded that the antigen is in considerable measure thermostable. The extractive antigens of the tubercle bacillus so far examined do then contain as a prominent feature of their makeup, alcohol soluble, thermostable substances.

The work of Much and his followers has been guided by the conception that the tubercle bacillus could furnish several distinct antigens mainly either protein, or lipin in their chemical relationships. Craig has reported exceptionally good numerical results by the use of an alcoholic extract of the tubercle bacillus as antigen. My observations touch the questions here involved in only one instance aside from the obvious general relationship indicated by the usual presence of an alcohol soluble active substance. I had at hand a considerable quantity of a toluol extract and suspension of tubercle bacillus. To this I added ten volumes of absolute alcohol which precipitated a considerable amount of solid matter. This was filtered through paper

and the filtrate was evaporated to approximately the original volume of clear reddish yellow fluid which no longer presented the distinctive odor of either toluol or alcohol. When mixed with ten volumes of normal salt solution this fluid gave a moderately stable emulsion of the type familiar to all as the emulsion of lipoids used as "antigen" in the Wassermann reaction. This emulsion proved to have considerable value as antigen with known tuberculous serum, a value not higher in the instance tested, however, than a number of other preparations. Used with known syphilitic sera it was demonstrated to be a very acceptable substitute for other forms of lipoid in the Wassermann reaction. This indicates that alcoholic extracts of the tubercle bacillus when of more than minimal lipoid concentration are to be viewed with caution in cases where syphilis has not been carefully excluded.

The thermostable properties of the tubercle antigen demand consideration from a very practical standpoint. Starting from the living tubercle bacillus to produce an antigen it would be of considerable advantage if these could be killed by heat as a first step. With this in mind a direct test was made of the effect of heat on an antigen consisting of an emulsion of the living bacillus in 50 per cent glycerin (assuming that the bacteria had not been killed by several days contact with glycerin).

Boiling for five minutes reduces both the anticomplementary and the antigenic value appreciably without destroying either. My data are not sufficient to enable me to decide whether the loss of antigenic value is of enough importance to warrant the retention of the complicating features of the presence (or possible presence) of the living bacillus in preparations made without the use of heat. Petroff (8) it should be noted, has recently obtained a very strong antigen by extracting the bacillus with boiling 25 per cent of glycerin. Whether anything is lost in this process which might advantageously be retained cannot at present be decided.

With this beginning it was evident that the use of the pooled preserved serum had enabled us to carry to a conclusion and with confidence experiments which would otherwise have been at the most fragmentary or suggestive. It is hoped that an extension of the line of experimentation employed, some of the still open questions relating to the properties of different cultures as antigens, specificity as to type, and the partial antigen question, may be susceptible of final solution.

With this information securely at hand it should be possible to fix upon one or more antigen preparations which could really be regarded as stable standards. From this point it might be hoped that the results in the study of cases during the progress of their disease could yield results of great value.

SUMMARY AND CONCLUSIONS

In the work here reported an effort has been made to apply quantitative methods to the study of the reaction of complement deviation in tuberculosis. The result has been to clearly confirm the observations of others that certain tuberculous individuals give strong deviation reactions. Others entirely fail to react. Certain persons to all intents and purposes normal give strong reactions also. The numerical relations are such as to make it unsafe to apply the complement deviation reaction to the diagnosis of tuberculosis except as a matter of the most limited confirmatory interest.

Continuous application of the reaction throughout the course of tuberculosis may have much interest and may in the future develop importance. My work so far contains no indications of value bearing on the significance of the reaction "in course" but the methods employed may eventually be advantageous to those undertaking observations of this kind.

The method of performing the test for complement deviation hitherto applied to tuberculosis studies has inherent defects which seriously impair its significance. These have been remedied to a considerable extent by increasing the time of the primary incubation or "period of fixation" to four hours and by employing several quantities of either complement or antigen simultaneously. By the latter feature minor fluctuations in activity which may often reverse the result at any single point stand revealed in their true significance. The increase in the fixation period allows the reaction to run more nearly to its end. Extension of the incubation beyond four hours might be advantageous, but is probably impossible because of the lability of the complement.

It has been found that a common feature of all of the "extractive" antigens made from the tubercle bacillus is a thermostable, alcohol soluble constituent. It has been shown that the antigenic activities of a suspension of tubercle bacilli are impaired but not destroyed by five minutes' exposure to a temperature of 100°C.

Advantage has been taken of the fact that the deviating qualities of tuberculous serums are reasonably well preserved by the addition of an equal quantity of glycerin, to establish a temporary standard for the determination of the qualities of antigens. It is probable that the further development of quantitative studies along these lines may be profitable.

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THE STERILIZATION OF LIPOVACCINES.

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The proposal to substitute suspensions of bacterial bodies in oil for suspensions in saline solution as a vaccine for use in combating typhoid fever and pneumonia theoretically offers great advantages. Provided the vaccination is safe and efficient, it would be of great importance to be able to get the same result with a single application that has, in the past, been accomplished with three doses of the prophylactic.

The evidence so far at hand would seem to show that the vaccination with oily suspensions causes a formation of antibodies comparable with that afforded by suspensions in water, and thus renders it probable that a similar degree of protection may be given by the lipovaccine. The matter is, however, of sufficient importance to justify repeated examination.

When material of this nature is to be widely distributed its sterility should be assured both by the method of preparation and control tests on the finished product. In this respect the methods proposed by Whitmore and Fennel[1] are not altogether satisfactory. The procedures recommended afford many opportunities for contamination, the oil interferes with the action of antiseptics so that these cannot be depended upon for a final sterilization, and lastly it is far from easy to make satisfactory tests for sterility on the finished product.

Rosenow and Osterberg,[2] recognizing these difficulties, propose to kill the bacteria and any contaminating organisms with a water solution of an antiseptic, to form an emulsion with the oil, and finally

[1] Whitmore, E. R., and Fennel, E. A., *J. Am. Med. Assn.*, 1918, lxx, 902.

[2] Rosenow, E. C., and Osterberg, A. E., *J. Am. Med. Assn.*, 1919, lxxiii, 87.

to remove the water by vacuum distillation at a comparatively low temperature. This appears from their statement to be an efficient method of preparation.

In approaching this matter we have followed another line of thought and wish to record our results at this time as a contribution to the subject without, however, attempting to decide which method may in the end be best.

Loeffler[3] has stated that by the application of dry heat bacteria may be killed without destroying their antigenic properties. The temperature he used was 70°C. and the exposure was prolonged for days or weeks. It is known that glassware and fabrics may be sterilized by exposure to dry heat for a number of hours, the length of exposure varying inversely with the temperature. Thus 130°C. for 3 hours is as efficient as 160°C. for 1 hour. The suspensions of bacteria in oil are essentially dry preparations, and it seemed possible that the finished vaccine could be sterilized at an intermediate temperature without destroying its antigenic qualities. As a matter of fact, our results indicate that this may be accomplished with pneumococcus. We have so far been unsuccessful with *Bacillus typhosus*.

EXPERIMENTAL.

Pneumococcus lipovaccine was prepared according to the method of Whitmore and Fennel.[1] Briefly, the bacteria were grown in glucose broth and separated by centrifugalization after about 18 hours growth. The bacterial mass was dried in an oven at 53°C. over lime. The dry mass was ground in a Pyrex jar with steel balls for a number of hours, a mixture of anhydrous lanolin and cottonseed oil (Wesson) added, and the grinding continued. Finally, sterile cottonseed oil containing 0.25 per cent chloretone was added in such amount that each cubic centimeter of the finished product would contain 2 mg. of the dried bacterial powder. The grinding was then continued for a number of hours, the product put into suitable bottles or ampules and sealed as ready for distribution.

Control tests for sterility revealed the presence of *Bacillus subtilis* and sometimes other bacteria in the dried mass in a majority of

[3] Loeffler, F., *Deutsch. med. Woch.*, 1913, xxxix, 1025.

instances. When the dried bacterial mass was clean the finished product was nearly always sterile. The pneumococcus does not survive the drying process. If the dried mass containing *Bacillus subtilis* is ground in oil containing chloretone this contaminating organism will remain viable for months. With experience in manipulation the amount of material lost because of contamination was reduced, but even with the greatest care it always remained high.

In an attempt to overcome this difficulty we exposed the finished vaccine to a temperature of 130°C. for 3 hours in an electric oven (Freas), and to 120°C. for 12 hours, temperatures which are sufficiently high to sterilize any material. The vaccine, heated and unheated, was administered to healthy mice (0.5 cc. subcutaneously), and after varying periods the resistance of the mice to pneumococcus infection was tested by intraperitoneal injection of doses of culture known to be fatal, or multiples thereof. The results of two experiments are given in Tables I and II.

The experiments show that a considerable degree of protection is afforded to mice by the administration of pneumococcus lipovaccine. In the occasional instances in which the vaccinated mice died it was found that the vaccine had not been absorbed, almost the whole mass injected remaining in the subcutaneous tissues. Protection is exerted against at least ten fatal doses of culture. The mice in the experiments reported had been treated with vaccine 35 and 38 days previously. In other experiments in which the interval was 21, 56, and 110 days, there was no evidence of protection, indicating that the immunity following a single dose of lipovaccine is slow to develop and is transient. The heat treatment did not decrease the antigenic qualities of the vaccine appreciably.

The administration of vaccine in practice as a prophylactic against pneumonia is still in the stage of trial. Since at present the qualities of typhoid vaccine are of much greater interest, we have extended our work to include this phase of the subject.

Typhoid lipovaccine[4] similarly heated and unheated was administered to rabbits intraperitoneally, a single dose of 1 cc. being given. The blood was tested for its agglutinin content at intervals there-

[4] The vaccines used in this experiment were obtained from the U. S. Army Medical School through the courtesy of Major H. J. Nichols.

TABLE I.

Protection Test of Mice Treated with Pneumococcus Lipovaccine.

The vaccinating dose was administered 35 days before the test. The test consisted of inoculation with the indicated quantity of a 24 hour bouillon culture injected intraperitoneally with normal salt solution sufficient to make a total volume of 0.5 cc.

Vaccine.	Culture.		Result.			
	Type.	Dilution.	After 24 hrs.	After 48 hrs.	After 72 hrs.	After 96 hrs.
None	III	1:10,000,000	Sick.	Sick.	Dead.	
	III	1:10,000,000	"	Dead.		
	III	1:100,000,000	"	"		
	III	1:100,000,000	Dead.			
	I	1:10,000,000	Sick.	Sick.	Dead.	
	I	1:10,000,000	Dead.			
	I	1:100,000,000	Sick.	Dead.		
	I	1:100,000,000	"	"		
Unheated	III	1:10,000,000	"	"		
	III	1:10,000,000	"	Sick.		Well.
	III	1:100,000,000	"	"		"
	III	1:100,000,000	Dead.			
	I	1:10,000,000	Sick.	Sick.		Well.
	I	1:10,000,000	Dead.			
	I	1:100,000,000	Sick.	Sick.		Well.
	I	1:100,000,000	Dead.			
Heated to 130°C. for 3 hrs.	III	1:10,000,000	Sick.	Sick.		Well.
	III	1:10,000,000	"	"	Dead.	
	III	1:100,000,000	"	"		Well.
	III	1:100,000,000	"	"		"
	I	1:10,000,000	"	"		"
	I	1:10,000,000	"	"		"
	I	1:100,000,000	"	"		"
	I	1:100,000,000	"	"		"
Heated to 120°C. for 12 hrs.	III	1:10,000,000	"	"		"
	III	1:10,000,000	"	"		"
	III	1:100,000,000	"	"		"
	III	1:100,000,000	"	"		"
	I	1:10,000,000	"	Dead.		
	I	1:10,000,000	"	Sick.		Well.
	I	1:100,000,000	"	"		"
	I	1:100,000,000	"	"		"

TABLE II.

Protection Test of Mice Treated with Pneumococcus Lipovaccine.

The vaccinating dose was given 38 days before the test. The test consisted of inoculation with the indicated quantity of a 24 hour bouillon culture of Type I pneumococcus intraperitoneally. The total volume injected was 0.5 cc.

Vaccine.	Dilution of culture.	Result.	
		After 24 hrs.	After 48 hrs.
None	1:1,000,000	Sick.	Dead.
	1:1,000,000	"	"
	1:1,000,000	Dead.	
	1:1,000,000	Sick.	Dead.
	1:1,000,000	"	"
	1:1,000,000	Dead.	
	1:1,000,000	Sick.	Dead.
	1:1,000,000	Dead.	
Unheated	1:1,000,000	Well.	Well.
	1:1,000,000	"	"
	1:1,000,000	"	"
	1:1,000,000	"	"
	1:1,000,000	Sick.	"
	1:1,000,000	"	"
	1:1,000,000	"	Dead.
	1:1,000,000	"	Well.
	1:1,000,000	"	"
Heated to 130°C. for 3 hrs.	1:1,000,000	"	"
	1:1,000,000	"	"
	1:1,000,000	"	"
	1:1,000,000	"	"
	1:1,000,000	"	"
	1:1,000,000	"	Dead.

after. As a control the results were compared with those obtained by the administration of three doses of typhoid vaccine in saline suspension intraperitoneally at 5 day intervals. The results are presented in Table III.

The experiment shows that at least for these particular preparations the lipovaccine is less efficient in single doses than is the saline preparation in three doses. The antigenic qualities of the lipovaccine (typhoid) are almost destroyed by heating to 130°C. for 3 hours.

TABLE III.

Agglutinin Production in Rabbits Treated with Typhoid Vaccines.

Rabbit No.	Interval since last dose.	Vaccine.	Serum dilution. 1:20	1:40	1:100	1:150	1:200	1:500	1:1,000	1:2,000	Remarks.
	days										
1	16	Saline.	++++	++++	++++	++++	++++	++++	+++	++	27 days after first dose.
2	16	"	++++	++++	++++	++++	++++	++++	+++	+	
3	16	"	++++	++++	++++	++++	++++	+++	++	0	
4	16	"	++++	++++	++++	++++	+++	++	+	0	
5	17	Lipovaccine I	++++	++++	++	0					Rabbits tested 12 days later show no increase in agglutinins.
6	17	" I	++++	++++	++++	++++	++	0			
7	17	" I	++++	++++	++++	++++	+++	0			
8	17	" I	++++	++++	++	0					
9	17	" II	+++	++	0						
10	17	" II	0	0	0	0					
11	17	" II	0	0	0	0					
12	17	" II	++++	+++	++	0					
		Lipovaccine heated to 130°C. for 3 hrs.									
13	16	Lipovaccine I	++	0	0						
14	16	" I	+++	+	0						
15	16	" I	+++	++	0						
16	16	" I	0	0	0						
17	16	" II	+++	++	0						
18	16	" II	0	0	0						
19	16	" II	++++	+++	0						
20	16	" II	0	0	0						

SUMMARY.

Pneumococcus lipovaccine confers a definite protection against pneumococcus infection in mice. The protective quality is not destroyed, and apparently is not greatly diminished, by heating to 130°C. for 3 hours or 120°C. for 12 hours.

Typhoid lipovaccine gives rise to the formation of agglutinins in rabbits but to a lesser degree than saline suspensions. The antigenic qualities of the typhoid lipovaccine are greatly injured by heating to 130°C. for 3 hours.

SOME EXPERIMENTS TO DETERMINE THE PERSISTENCE OF EXTRANEOUS BACTERIA IN THE GASTRO-INTESTINAL TRACT OF GUINEA-PIGS AS INFLUENCED BY DIET*

A. GRAEME MITCHELL, M.D., AND PAUL LEWIS, M.D.

PHILADELPHIA

INTRODUCTION

It is commonly believed that the character of the bacterial flora of the gastro-intestinal tract has an important influence on health. In certain instances this is unquestioned. The implantation of sufficient numbers of certain bacteria, *B. typhosus, B. dysenteriae* or *Vibrion cholerae* in the absence of a counteracting general bodily immunity brings about the development of the infections specifically related to these organisms. So also, but possibly in a less specific way, the less well characterized gastro-intestinal disturbances of infancy and childhood are commonly supposed to be due either to the activity of particular species of bacteria or to an alteration in prevailing types of micro-organisms.

A relationship between the general type of bacterial flora prevailing in the gastro-intestinal tract and more obscure disorders, such as anemias and ill defined general intoxications, is often surmised, but scientific evidence of such an association cannot be said to have been presented convincingly. None the less, the administration of acid producing types of bacteria with the conception that they will be of benefit in limiting the activity of putrefactive types is widely practiced. A review of the literature leaves it a matter of great doubt whether the administration of the acid producing types leads to more than a most temporary change in the intestinal flora. The experiments of unbiased observers make it probable that after a short period the extraneous bacteria are completely eliminated. Assuming that the prevalence of a type of micro-organism or of a particular species is of favorable significance for the host, it becomes a matter of considerable interest to know on what condition or circumstance the survival of the favored type is possible.

This question is closely related to another of the same general character and of equal importance, namely, the periodic variation in the prevailing type of bacteria in the respiratory tract. Not that the

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causes of variation in the respiratory tract are likely to be identical with those in the intestine, but the principles on which these variations take place are likely to have important common features.

The problems involved are of great interest from a biologic point of view. A complete solution of them would doubtless influence practice. What our work has to offer, however, is not a solution—merely a beginning—and a suggestion as to a method of study not previously employed. The work here presented is in a sense an extension of experiments carried out some years ago by one of us (Lewis, unpublished) in the course of which the method of study was used and some of its limitations defined. Aside from outlining a method and the conditions met with as preliminary to experimentation in this field our present paper offers one point which seems to have real interest, namely, that while *B. pyocyaneus* quickly disappears from the normal gastro-intestinal tract on a normal diet, and does not persist longer when certain obviously unfavorable diets are offered, the addition of certain favorable factors (greens) to an otherwise unsatisfactory diet does tend to favor the persistence of this organism. This may warrant the suggestion that the relationships between particular bacterial species as persistent inhabitants of the intestinal tract and particular articles of diet may be closer than has hitherto been postulated, and this idea may be worthy of further study.

REVIEW OF LITERATURE

The intestinal flora of man and other animals has been studied extensively, and has been of especial interest to the pediatrist. Not only have the types of bacteria been investigated in various intestinal disorders, but the "switching" from a predominance of one type to another has been demonstrated.[1] Briefly stated, an excess of carbo-

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hydrate in the diet tends to favor the growth of the acid forming type of bacteria in the intestinal tract, while an excess of protein favors the growth of putrefactive organisms.

Some of Metchnikoff's pupils and followers have published investigations that attempt to support his hypothesis that the lactic acid bacillus is implanted in the digestive tract. Cohendy [2] concluded from the study of four human subjects that the *B. bulgaricus* appeared in the stool from three to five days after the first ingestion of that organism. It was found each day thereafter, and it was still present in the stool from twelve to twenty-four days after the last ingestion. In one of these patients it was revealed by an abdominal operation, which occurred during the course of the experiment, that the *B. bulgaricus* multiplied in the upper two-thirds of the colon. Results similar to these were obtained by Leva.[3] Later Cohendy experimented with thirty other subjects, including himself. In this later work he apparently did not attempt to recover the ingested organism from the stool.

Belonovsky [4] conducted experiments on mice over a period of ten months. After feeding the bulgarian ferment daily to these animals, he recovered the organism in ten days by culturing the stool, and found that it persisted in the intestinal discharges for about four weeks after the return to a normal régime and the cessation of germ feeding. The author states that on examining the excrement under the microscope, there was no predominance of the bulgarian bacillus. Control mice were fed various substances, such as lactic acid, sterilized milk, bulgarian ferment killed by heat, and other organisms (*B. pyocyaneus* and *B. prodigiosus*). It was only in mice fed with *B. bulgaricus* that the total number of bacteria in the droppings was diminished. It was apparently on such evidence as this that Metchnikoff based his claim of intestinal implantation of the bulgarian bacillus, as he himself does not seem ever to have demonstrated such a phenomenon.[5]

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5. Metchnikoff, E., et al.: Bacteriotherapie, Vaccination, Serotherapie, J. B. Bailliere et Fils, Paris, 1909. Metchnikoff, E.: The Prolongation of Life, New York, Putnam Sons, 1908. Etudes sur la Flore Intestinale, Ann. Inst. Pasteur **27**:894, 1913. We are not concerned here with the question as to whether or not the feeding of the bacillus does good clinically. The subject under discussion is only that of the implantation of organisms in the intestinal tract.

The work of later investigators does not substantiate the theory of implantation.[6] Hull and Rettger performed one hundred and eighty individual experiments on white rats, six on other laboratory animals, and four on man. They collected and cultured the feces, but were unable to establish the *B. bulgaricus* in the intestinal tract, in spite of the ingestion of large numbers of these organisms. Herter and Kendall found that the exclusive feeding of a rhesus monkey for two weeks with milk fermented with the bulgarian bacillus failed to establish the predominance of this organism in the cecal region or in the colon. The experiments of Rahe show that the bacillus bulgaricus is capable of an apparently limited survival in the upper intestine of the monkey. Rahe's results are shown in Table 1.

TABLE 1.—Results of Feeding B. Bulgaricus to Monkey

Monkey	Fed	Period of Ingestion	Time Killed after Last Ingestion	Duodenum	Jejunum	Ileum	Cecum	Feces
1	50 tablets per day.....	13 days	24 hours	—	+	—	—	—
2	300 c.c. 48-hr. milk culture.	6 days	7 hours	+	+	+	+	+
3	300 c.c. 48-hr. milk culture.	6 days	7 hours	+	—	—	—	—

More recently the *B. acidophilus,* a normal inhabitant of the intestinal tract of man, has been introduced by mouth in order to prevent the proliferation of the proteolytic types of organisms. It may be said, however, that the proof of the implantation of organisms in the intestinal tract of man or of laboratory animals rests on incomplete evidence.

METHOD OF PROCEDURE

We have approached this subject from a somewhat different angle than previous investigators. The present study is concerned only with the attempt at implantation of an extraneous organism, the *B. pyocyaneus,* in the digestive tract of the guinea-pig. Our aim has been to study the principles governing the implantation, if such can be accomplished. If implantation should not be found possible, we may hope to find out the reasons back of this local immunity. *B. pyocyaneus* has several advantageous characteristics for a study of this kind: it is potentially pathogenic; it produces poisonous substances

6. Rahe, A. H.: A Study of the So-Called Implantation of the Bacillus Bulgaricus, J. Infect. Dis. **16**:210, 1915. Editorial, J. A. M. A. **73**:1844 (Dec. 13) 1919. Herter, C. A., and Kendall, A. I.: An Observation on the Fate of Bacillus Bulgaricus (in Bacillac) in the Digestive Tract of a Monkey, J. Biol. Chem. **5**:293, 1908. Luerssen, A., and Kuhn, M.: Yoghurt, die Bulgarische Saurmilch, Centralbl. f. Bakteriol. **20**:234, 1908 (Quoted by Hull and Rettger, J. Bacteriol. **2**:47, 1917. Heinemann, P. G.: Lactic Acid as an Agent to Reduce Intestinal Putrefaction, J. A. M. A. **52**:373, 1909.

in culture which in its pathogenic relationships it assumes in various character, and above all it is easy of recognition.

The guinea-pig has a comparatively sterile gastro-intestinal tract. This may readily be proved by killing a guinea-pig after a twenty-four hours' fast and taking smears and cultures from the various parts of the intestinal segments. One usually finds a moderate number of organisms in the smear from the stomach; often none from the duodenal smear; a rather large number from the ileum, cecum and colon. Cultures made on agar will frequently show no growth. This negative finding is especially constant in the duodenum. Such a distribution of bacteria corresponds to that found in the intestinal tract of man.[7] If the pig has not been in a state of fast and has a gastro-intestinal tract full of food, organisms found by smear and culture are more numerous, and different molds introduced with the food may grow in the culture. Again, if some time has elapsed between death and the taking of the smears and cultures, the organisms will be correspondingly numerous. The organisms found are gram-positive and gram-negative diplococci and bacilli, the types varying with the diet. (Cultures taken in the manner described show, of course, only the aerobic bacteria). It is possible for certain animals to live with sterile digestive tracts.[8]

The *B. pyocyaneus,* as far as we have been able to ascertain, is not a normal inhabitant of the gastro-intestinal tract of the guinea-pig. Furthermore, this organism has a low pathogenicity, for the guinea-pig can be fed in large numbers mixed with the food without causing ill effects. If fed in the manner as described it seldom enters the blood stream and causes a septicemia. It may, however, gain entrance to the circulation through the intestinal tract.[9] The *B. pyocyaneus* occasionally occurs in the digestive tract of the human apparently in the best of health. In some of our earlier experiments we introduced the *B. pyocyaneus* into the stomach of the guinea-pig by means of a small catheter used as a stomach tube. When a considerable number of organisms were introduced in this manner, the animal died exhibiting a violent gastro-enteritis and a growth of the bacillus was obtained

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7. Contributions to the Science of Medicine by the Pupils of William Welch, 1900, p. 543, Cushing and Livingood.

8. Nuttall, G. H. F., and Thierfelder, H.: Thierisches Leben ohne Bakterien im Verdauungskanal, Ztschr. f. Physiol. Chem. **21**:109, 1895; **22**:62, 1896; **23**:231, 1897. Wolmann, E.: Sur l'elevage des Mouches Steriles, Ann. Inst. Pasteur **25**:79, 1911. Cohendy, M.: Experiences sur la Vie sans Microbe, Ann. Inst. Pasteur **26**:106, 1912. Bakteriologische Darmuntersuchungen. Skand. Arch. f. Physiol. **16**:249, 1904. Freeman, L.: Chronic General Infection with Bacillus Pyocyaneus, Tr. Am. Surg. Assn. **34**:113, 1916.

9. Freeman, L.: Chronic General Infection with the *Bacillus Pyocyaneus,* Tr. Am. Surg. A. **34**;113, 1916.

from the heart blood. If, however, no *B. pyocyaneus* could be recovered from the gastro-intestinal canal, no evidence of gastro-enteritis was observed when the animal was killed, and the culture from the heart was negative. This method was given up, for the time being at least.

TECHNIC

With the exception of these experiments the technic of the study was as follows: Guinea-pigs that were offered various diets were fed the *B. pyocyaneus* for variable lengths of time. Later, in order to make the experiments uniform, all the pigs were fed the germ for three days. A fresh twenty-four hour culture of a strain of the *B. pyocyaneus* which produced a brilliant green color was washed from an agar slant with about 5 c.c. of physiologic sodium chlorid solution and thoroughly mixed with the day's supply of food for the pig. On cessation of the feeding of *B. pyocyaneus,* nourishment of the pig continued with the various diets unmixed with the organism. At variable lengths of time the pigs were killed and cultures made on agar from the heart blood, the stomach, the duodenum, the ileum, the cecum and the colon. If the pig died the same cultures were made. These cultures were incubated for twenty-four hours, and after that kept at room temperature. No tube was declared negative for the *B. pyocyaneus* until at least five days had elapsed without evidence of green pigmentation. After having first ascertained that it was the *B. pyocyaneus* with which we were working, an appearance of the green pigment was considered sufficient evidence of the presence of that organism in the cultures. The + marks in the charts indicate the amount of green pigmentation appearing in the agar, + a small amount of the color; ++ a larger amount, coloring about half the agar slant; +++ when all the agar was permeated with the pigment.

A series of experiments was first undertaken to ascertain whether or not the *B. pyocyaneus* would grow in the gastro-intestinal tract of the guinea-pig, and whether or not diet had any effect on such growth. Previous to the feeding of the *B. pyocyaneus* mixed with the food, the pigs had been fed on their regular diet which consisted of oats and bread mixed with water, hay, and green stuff twice a week. Of the fourteen pigs used, three were continued on their regular diet and the *B. pyocyaneus* was mixed with the oats, bread and water for two days. *Bacillus pyocyaneus* was recovered from the cecum of two of these pigs when killed one or two days later, but not from the pig killed four days later. The remaining pigs in this series were kept on their regular diets until the day on which they received their first *B. pyocyaneus* feeding mixed with their new diets. They did not take the abnormal diet well, and there is, therefore, some doubt

as to the amount of germ ingested. However, in three of these pigs the *B. pyocyaneus* was recovered either from the ileum or cecum or both, when killed two days after having been previously fed *B. pyocyaneus* for two days. These three pigs had been fed on hay and water, milk and water, and crackers and water respectively. Other pigs in this series had been nourished on crackers and milk, bread and milk, bread and water, oats and water. From the pigs thus fed *B. pyocyaneus* could not be recovered when they were killed two days after the cessation of a two day period during which that organism had been administered with the food.

In order to find out whether the length of time during which the *B. pyocyaneus* was fed had any effect on its persistence in the digestive tract, several pigs were fed with the organism mixed with their regular diet for variable lengths of time (from three to fourteen days) and then killed at intervals of from two to eleven days. In none of these pigs was the *B. pyocyaneus* recovered when cultures were taken from the different parts of their intestinal tract and stomach (Table 2).

TABLE 2.—Results in Pigs Fed on Normal Diet of Oats, Hay, Bread and Green Stuff. B. Pyocyaneus Mixed with This Normal Diet for Variable Lengths of Time. Normal Diet Continued Until Pigs Were Killed or Died

No. Days Pigs Fed	Killed or Died	Day Killed or Died	Heart Culture	Stomach Culture	Duodenum Culture	Ileum Culture	Cecum Culture	Colon Culture
2	K	1	.....	0	0	0	+	
2	K	2	.....	0	0	.....	+	
2	K	4	.....	0	0	0	0	
3	K	4	.....	0	0	0	0	0
3	K	5	.....	0	0	0	0	
3	K	6	N.G.—0	0	0	0	0	0
3	K	7	.....	0	0	0	0	0
3	K	8	N.G.—0	0	0	0	0	0
3	K	9	N.G.—0	0	0	0	0	0
3	K	11	N.G.—0	0	0	0	0	
7	K	3	.....	0	0	.....	0	
14	K	2	N.G.—0	0	0	0	0	0

Day killed or died, i.e., day after last ingestion of pyocyaneus. In the columns showing the results of culture, a blank indicates that no culture was taken; O indicates that there was no growth of pyocyaneus; N.G. indicates that there was no growth or any type of organism; + indicates a growth of pyocyaneus.

The thought presents itself as to whether or not much of the pyocyaneus is ingested when the organism is mixed with the regular diet of oats, bread and water, hay and green stuff. It will be remembered that in eating the whole oat the pig cracks open the outer covering of the oat kernel, discards this covering and eats the softer center. By using rolled or crushed oats the culture of *B. pyocyaneus* can be mixed thoroughly with the food. Accordingly, four pigs were fed in this manner. First, they were given a two-day diet of rolled oats without pyocyaneus. This was to accustom them to their diet, or

at least to assure sufficient hunger so that during the three following days in which the *B. pyocyaneus* was fed a considerable amount of the germ-mixed food would be ingested. On discontinuing the feeding of the organism, the regular diet was instituted. The *B. pyocyaneus* was not recovered from any of the pigs of this series when killed at intervals of from five to eleven days later. On the normal diet, *B. pyocyaneus* does not, then, persist in the digestive canal.

Several other experiments were carried out, the details of which need not be given. Briefly, they consisted in feeding series of pigs on a simple died of oat kernels and water. In some of these series the attempt was made to assure the ingestion of the bacillus by mixing it with oats and water eighteen hours or less before feeding. It was found that the organism did not always live under such circumstances.

TABLE 3.—Pigs Fed Rolled Oats for One Week; Then Rolled Oats Plus B. Pyocyaneus for from One to Three Days. A Diet of Rolled Oats Was Then Continued. Three Controls Not Fed B. Pyocyaneus Died at Eight, Eight and Fifteen Days, Respectively

No. Days Pyo. Fed	Killed or Died	Day Killed or Died	Heart Culture	Stomach Culture	Duodenum Culture	Ileum Culture	Cecum Culture	Colon Culture
3	D	2	+++	+++	.....	.....	++	
3	D	2	N.G.—0	+++	.....	.....	+++	
3	D	3	N.G.—0	0	0	.....	++	0
3	K	5	N.G.—0	0	0	.....	0	0
3	K	7	N.G.—0	+++	++	0	++	+
1	D	1	N.G.—0	0	0	0	0	0
2	D	2	N.G.—0	++	++	++	+++	++
3	D	3	+++	+++	N.G.—0	+++	+++	+++
2	D	4	N.G.—0	++	++	++	0	
3	D	3	N.G.—0	+	0	++	+++	0
2	K	7	.....	0	N.G.—0	0	0	N.G.—0
2	K	9	.....	0	0	.....	0	0
3	K	9	.....	+	++	.....	0	0
3	K	9	.....	0	0	0	0	0

\+ Indicates a slight growth of pyocyaneus.
++ Indicates a more active growth.
+++ Indicates a large amount of growth.

In order to remove doubt as to whether the *B. pyocyaneus* was ingested because of the failure of the pigs to eat an abnormal diet, such as rolled oats, a number of pigs were fed *B. pyocyaneus* only after they had been previously fed on rolled oats alone for a week. Over 50 per cent. of the fourteen pigs in this series died.[10] We believe that it is seldom, if ever, that guinea-pigs die as the result of the ingestion of *B. pyocyaneus* when mixed with the food, but that death is due rather to the lack of essential elements in the limited diet. It will be seen later that the addition of green stuff to the rolled oats partly overcame this difficulty, and that only four of fifteen pigs

10. Three control pigs that were fed simply on rolled oats and water without at any time the admixture of *B. pyocyaneus* died at eight, eight, and fifteen days, respectively, after the institution of the régime.

(about 25 per cent.) died. It is probable from the necropsy findings and the cultures that at least two of these four pigs died from an infection with an organism of the paratyphoid group. *B. pyocyaneus* was recovered from the gastro-intestinal tract of nine of the fourteen pigs (Table 3). Three of these nine pigs died two days after the cessation of pyocyaneus feeding; three died three days after; one died four days after; one was killed seven days after and one was killed nine days after. Of the five pigs in which the *B. pyocyaneus* was not recovered one died at the end of the first day after the attempt to feed *B. pyocyaneus* and this pig was apparently sick at the time with an infection by an organism of the paratyphoid group and did not eat the food mixed with the *B. pyocyaneus*. Of the other four, one was killed at the end of five days, one at seven days and ten at the end of nine days.

In the next experiment a small amount of green stuff was added each day to the rolled oats diet. *B. pyocyaneus* was recovered in all at the end of seven days after the cessation of *B. pyocyaneus* feeding, one was killed nine days after feeding ceased and one was killed thirteen days after feeding ceased. Of the pigs in which *B. pyocyaneus* was recovered, two died the first day after the cessation of pyocyaneus feeding; one was killed after five days; one was killed and one died after seven days; one was killed at eight days; three were killed at nine days; one was killed at ten days; one was killed at eleven days and one was killed at twelve days (Table 4).

TABLE 4.—Pigs Fed Rolled Oats Plus Green Stuff for Five Days; Then Rolled Oats Plus Green Stuff Plus B. Pyocyaneus for from Two to Three Days. A Diet of Rolled Oats and Green Stuff Then Continued

No. Days Pyo. Fed	Killed or Died	Day Killed or Died	Heart Culture	Stomach Culture	Duodenum Culture	Ileum Culture	Cecum Culture	Colon Culture
2	D	1	N.G.—0	+++	+++	.....	[illegible]	+++
2	D	1	0	+++	+++	+++	+++	0
3	D	7	N.G.—0	+++	0	++	[illegible]	+
3	D	10	N.G.—0	+	0	.....	++	++
3	K	5	+	0	N.G.—0	[illegible]	+	0
3	K	7	N.G.—0	0	0	0	0	
3	K	7	N.G.—0	N.G.—0	.....	0	+	N.G.—0
3	K	9	.....	0	0	0	+++	0
3	K	9	N.G.—0	+++	+	0	0	0
3	K	9	N.G.—0	0	0	0	+	
3	K	9	N.G.—0	0	0	0	0	0
3	K	9	N.G.—0	0	0	0	++	0
3	K	10	N.G.—0	+	0	.....	++	++
3	K	11	N.G.—0	0	0	0	++	0
3	K	12	N.G.—0	0	N.G.—0	0	+	0
3	K	13	N.G.—0	0	N.G.—0	0	+	0

Ten pigs were now fed rolled oats and butter for five days, then *B. pyocyaneus* was mixed with this food for three days and the rolled oats and butter diet continued thereafter. In all of this series *B.*

pyocyaneus was recovered from the digestive tract when the pigs were killed or died from three to thirteen days following the cessation of germ feeding. Five pigs died at three, four, seven, nine and ten days, respectively, and five were killed at five, five, seven, eleven and thirteen days respectively (Table 5).

TABLE 5.—Pigs Fed Rolled Oats Plus Butter for Five Days; Then Rolled Oats Plus Butter Plus B. Pyocyaneus for Three Days. A Diet of Rolled Oats and Butter Was Then Continued

Killed or Died	Day Killed or Died	Heart Culture	Stomach Culture	Duodenum Culture	Ileum Culture	Cecum Culture	Colon Culture
D	3	N.G.—0	0	+	+++	+++	0
D	4	N.G.—0	0	0	.....	+++	N.G.—0
K	5	N.G.—0	N.G.—0	N.G.—0	.....	++	0
K	5	0	0	0	++	+++	+++
D	7	N.G.—0	++	++	0	++	++
K	7	0	0	0	N.G.—0	+	0
D	9	N.G.—0	+	+++	++	++	0
D	9	N.G.—0	++	++	0	+	0
K	11	N.G.—0	0	N.G.—0	.....	+++	0
K	13	N.G.—0	+	++	+	+	++

SUMMARY AND CONCLUSIONS

Bacillus pyocyaneus when fed to guinea-pigs nourished on a diet of oats, hay, bread and green stuff (the normal diet in this laboratory) usually disappears from the gastro-intestinal tract within three days. When oat meal is given as a sole article of diet, the *B. pyocyaneus* has been found at seven and nine days after the last administration. The addition of a small amount of green stuff, or of a certain amount of butter to the oatmeal diet, has apparently prolonged the period of persistence of the bacterium: *B. pyocyaneus* on these slightly amplified diets has been found to persist about two weeks with considerable regularity. This increased persistence is probably apparent only. The animals on a strict oatmeal diet do not live long enough to enable a complete experiment to be carried out much beyond eight or ten days.

Bacillus pyocyaneus could not be recovered from the digestive canal in any case more than sixteen days after the cessation of its ingestion by mouth. Judged by the amount of pigment produced in the culture, the number of surviving bacteria became progressively less the longer the time interval following the cessation of its ingestion by the pig. *B. pyocyaneus* persisted more readily in the cecum than in other parts of the digestive tract, next in the stomach, although it was often found on culturing the duodenum, ileum and colon. This was true whether the pigs were killed soon after the cessation of *B. pyocyaneus* feeding or only after a longer interval.

It is probable, on the basis of these experiments, that there is an effect of dietary deficiency which consists in the depression of a normal mechanism controlling the implantation of extraneous bacteria in the intestinal tract.

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THE X-RAY FLUORESCENCE OF CERTAIN ORGANIC COMPOUNDS.

By H. S. Newcomer.

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In a previous[1] paper I pointed out that it might in the future become possible to make use, biologically, of a localized transformation of penetrative radiant energy with very feeble abiotic properties (X-ray), into a much more active, although less penetrative type of ray (ultra-violet) through fluorescent substances as intermediaries. It was shown, in fact, that fluorite under the influence of the X-ray emitted bactericidal rays. Progress from this point demanding that we have for use in place of the insoluble fluorite a similarly active soluble substance, a survey was made of a large number of substances, for the most part organic chemicals, to see which of them might fluoresce under the influence of the X-ray.

Kunz and Baskerville[2] have examined the action of radiation on 13,000 minerals in the collection of the American Museum of Natural History. Their most noteworthy observations were the variability in like minerals

[1] H. S. Newcomer, *J. Exp. Med.*, **26**, 675 (1917).

[2] G. F. Kunz and Chas. Baskerville, *Science*, **18**, 769 (1903).

from the same source. There would seem to be 2 types of fluorescence, a specific type characteristic of the substance such as is found in the case of fluorite and a nonspecific type variably associated with the substance as in the case of willemite, hyalite, gypsum, etc. Others publishing literature on X-ray fluorescence are Edison,[1] Burbank,[2] Arnold,[3] and Precht,[4] Wiedemann and Schmidt.[5]

Pohl[6] has determined the amount of energy transformed into fluorescent light by barium platinocyanide and by calcium wolframite and finds it to be 3.7%. McIlkney[7] states that calcium tungstate crystals emit light whose wave length is further toward the ultra-violet the smaller are the crystals. The range is given as from the yellow to the ultra-violet border.

Our examination included both visual and photographic observations. The purpose of the latter was to detect any invisible ultra-violet radiation which might be developed, the ordinary photographic plate being uniformly sensitive from about 5000 Ångstrom units (blue-green), down to 2200 Ångstrom units, quite far out into the ultra-violet. The X-rays fell horizontally on the compounds arranged 6 at a time in separate black pasteboard compartments directly beneath a Graflex plate; the plate being protected from the action of the X-rays by a $^1/_2$-inch block of lead in its plane. The exposures were for 2 minutes. The solid compounds were placed in black paper containers, the liquids in 30 cc. "Nonsol" beakers, the photographic effect of whose fluorescence was practically nil.

In order to determine the presence of visible fluorescence the eyes were first thoroughly dark-accommodated and kept so, assistants doing all the handling of the materials. The solids were placed on black sheets of paper, the liquids in paraffined paper cups, the fluorescence of which was barely within the limits of visibility.

The X-ray tube was entirely enclosed. The rays passed through, besides the glass of the tube itself, a layer of black paper. All of the compounds were also examined with the additional interposition of a one mm. aluminum screen. The effect of the screen was to reduce slightly the intensity of the fluorescence observed.

The machine was a Victor fluoroscopic outfit of 1500 watts capacity, having a Coolidge fine focus tube. The distance of the compound from the anticathode was 22 cm. The machine was run at about a maximum

[1] Thos. Edison, *Elec. Rev.*, **165**, 53 (1896).
[2] J. J. Burbank, *Amer. J. Sci.*, **155**, 53 (1898).
[3] W. Arnold, *Ann. physik. Chem.* n. f., **61**, 313 (1897).
[4] J. Precht, *ibid.*, **61**, 330 (1897).
[5] E. Wiedemann and G. C. Schmidt, *ibid.*, **56**, 201 (1895).
[6] R. Pohl, "Die Physik der Röntgenstrahlen," Braunschweig, **1912**, 147.
[7] P. C. McIlkney, *Elec. World*, **28**, 664 (1896).

continuous load, the energy delivered varying slightly from time to time, but being maintained so as to give a maximum illumination of the fluorescing screen of the outfit, the existence of such a maximum being frequently checked. As the machine did not have good meters the exact conditions were not known, but the current across the tube was about 15 milliamperes and the potential about 55,000 volts, these figures being checked by later measurements in which the conditions of the experiment were reproduced.

There is good reason for believing that maximum fluorescence is produced by a maximum delivery of X-ray energy, or that within a considerable range the fluorescence is independent of the quality of the X-rays and proportional to the energy alone. Several experiments were set up, using a much larger machine and a new Coolidge tube in which a fluorescent screen, indeed several screens, were radiated without the interposition of anything between the screen surface and the X-ray tube except black paper, selective absorption of the softer rays, especially by aluminum, being avoided. Using various potentials across the tube the current was so adjusted as to produce a certain definite faint fluorescence in the screen, the intensity of the fluorescence being taken such as to make variations most perceptible. The current was read on a milliammeter and the voltage computed from the alternative spark gap between 1.9 mm. polished steel balls.[1,2] It was found that with the intensity of the fluorescence judged constant the product of the milliamperage and the square of the potential was approximately constant, that is, the energy was constant. The potential range was from about 10,000 to 70,000 volts. Within some such range the fluorescence is thus independent of the X-ray wave length and dependent on the energy alone. So far as I can determine the quality of the fluorescence, its color, is dependent on the substance alone and not on the quality of the X-rays.

The compounds used were not specially purified. The larger number of the organic compounds were imported commercial samples. Some were prepared in the laboratory in the course of the synthesis of dyes. The dyes were mostly of German origin.

It is well known that slight impurities may determine the character of fluorescence. Fluorescence is, however, not necessarily associated with the presence of impurities. Of the compounds listed in Table II only the fluorescence of the amino acids seems to have been due to the presence of impurities. In general, compounds of different origin and occasionally even of different appearance behaved alike under the X-rays. Occasionally small particles of presumably foreign material were observed as brightly shining specks in an inert material.

[1] F. E. Fowle, *Smithsonian Inst. Pub.*, **63**, 2269 (1918), No. 6.

[2] G. W. C. Kaye and T. H. Laby, "Tables of Physical and Chemical Constants and some Mathematical Functions," London, 1916.

In recording the visual effect produced by the fluorescence it was convenient to take 1+ as the minimum of light that could be seen with certainty and 8+, corresponding to the luminosity of the several diamonds which were tried, as the maximum luminosity observed. It was found possible to recognize differences repeatedly in this scale. It was, of course, necessary to consider only the surface brightness of the substance and not the total quantity of light which a large body might emit. The recording of visual intensity is somewhat unsatisfactory because its apparent amount is so closely connected with its color. The dark-accommodated eye is most sensitive to light of wave length about 5400 Ångstrom units (green). Its sensitivity varies much with the color and in its region of maximum sensitivity it can detect light many times fainter than that in any region necessary to affect the photographic plate.

All of the compounds which affected the photographic plate were studied spectrographically. They were placed in paste-board containers before a 3 mm. slit of a quartz spectrograph (size C, Adam Hilger), and X-rayed for 2 hours. Eastman Graflex plates were used. Allowing for the distortion due to the wide slit, Table I gives the wave lengths and general characteristics of the fluorescent light so analyzed.

The result of the survey is to show that many organic compounds, whether solid or liquid, fluoresce under the X-ray. This fluorescence lies more commonly in the violet, blue and green parts of the spectrum. It is rarely sufficiently strong to affect a photographic plate. It is often at the violet-ultra-violet border. It seems probable that in approaching the far ultra-violet fluorescence becomes less common. A set up to determine the existence of a fluorescence of wave length appreciably less than 2000 Ångstrom units would be extraordinarily difficult and tedious to execute. Fluorescence is again common in the region of the X-ray spectrum.

As a rule liquids, amorphous colored substances (dyes) and substances in solution, when they are fluorescent, are feebly so and the conditions as to the observation must be rigid, particularly in respect to darkness and accommodation. Solutions in water of fluorescing solids have in some instances been tried. These solutions have been faintly fluorescent. The faintness is in part accounted for by the dilution of the material. It does not seem to be proportional to the dilution, but no extended study has been made of this question. Amorphous colored compounds seem to be distinctly less fluorescent than closely related but distinctly crystalline substances. There are, however, many colorless amorphous substances which fluoresce brightly. Most of them are inorganic compounds, in fact the most brightly fluorescing compounds are inorganic Many of those substances which give off bright and often distinctly colored light when subjected to ultra-violet radiation give off light just as strongly under the influence of X-rays. The ordinary luminous watch is a good

example. It is interesting that the air is very faintly fluorescent under the action of X-rays. Certain compounds were found to be distinctly phosphorescent.

The results of this work when assembled are apparently not susceptible of rational classification based on chemical relationships. They are, therefore, arranged in two tables, II and III, giving the visible fluorescence observed.

Sodium bromide is the only substance found which emits rays of wave lengths which we know to be bactericidally active (below 2800 Ångstrom units). Of organic compounds certain phenols and other benzene derivatives approach this most closely. Visible fluorescence of considerable intensity without effect on the photographic plate was found quite commonly among derivatives of benzol, particularly benzoic acid and its relatives and among the naphthalene derivatives.

TABLE I.

Substances Affecting the Photographic Plate.

Compound.	Wave length of the fluorescence in Ångstrom units.	Visible fluorescence.	Intensity and the position of the maxima and minima.
Potassium iodide	4400–4750	Moderate	Peak at 4550, very faint.
Potassium bromide	4200–4900	Bright	Peak at 4650, faint.
Sodium bromide	2400–5000	Bright	Strong, extends beyond these limits in both directions. Broad region of slightly diminished intensity at 4000.
Strontium salicylate	3950–4900	Bright	Symmetrical, fairly strong
Benzoic acid	2950–5000	Moderate	Not strong, region of diminished intensity at 3900.
p-Sulfone-amine-benzoic acid	2950–3500	Bright	Peak at 3200, faint.
Phenol	2960–5000	Moderate	Strong, peaks at 3080 and at 4850. Broad region of diminised intensity at 3500.
p-Amidophenol hydrochloride	2950–3350	Moderate	Not strong, peak at 3050.
Diphenyl	3450–4500	Bright	Flat even distribution, fairly strong.
Naphthalene	3300–4500	Moderate	Strong, peak at 3460.
β-Naphthalene sodium sulfonate.	3300–4900	Bright	Broad peak at 3900, fairly strong.
β-Naphthalene sodium sulfonate, purified crystals	3300–5000	Bright	Peak at 3500 sloping gradually to the visible, fairly strong.
Naphthalene calcium disulfonate.	3700–4500	Moderate	Faint.
Sodium naphthionate	4100–4700	Bright	Faint.
2,6-β-Naphthol ammonium sulfonate	3700–5000	Bright	Not strong, even.

NOTE.—It is possible that of the other substances listed in Table II there is also a photographic effect from *o*-hydroxybenzoic acid; sodium *o*-hydroxybenzoate; *o*-aminobenzoic acid; benzidine and hexamethylene tetramine triguaiacol.

TABLE II.[1]

The Visible Fluorescence of Organic Compounds.

Substance.	Visibility.	Substance.	Visibility.
acetamide	0	hydrazo-benzene	0
acetanilide	3	diazo-aminobenzene	0
methyl-acetanilide	2	bromobenzene*	2
acetone*	3	*o*-bromo-nitrobenzene	2
acridine	4	ethyl benzene	0
phenyl-acridine	7	iodobenzene*	2
alanine	0	iodosobenzene-*p*-sulfonic acid	4
phenyl-alanine	2	benzene ethylsulfonate	0
phenyl-alanine (from casein)	3	benzene-*m*-sodium disulfonate	8 P
phenyl-alanine hydrochloride	2	benzophenone	7
sodium alizarin sulfonate	0	benzil	6
aminoid peptone		benzyl alcohol*	0
(amino acid N = 60%) beef	0	benzyl aniline	2
aminoid peptone		benzyl chloride*	1
(amino acid N = 50%) casein	2	benzyl cyanide*	3
aminoids (biuret free)		benzyl ethyl ether*	2
casein	0	benzoyl acetone	2
aminoids (biuret free)		benzonitrile*	3
beef	0	benzoyl thymol*	1
amino acid still-residue	1	benzidine	6
diamino-stibene	0	benzidine C	1
amyl alcohol*	1	benzidine 2 H acid	0
iso-amyl iodide*	0	benzidine poly-iodo-acetate	0
aniline*	0	benzidine sulfone	1
diethyl-aniline*	2	benzidine sulfone	
dimethyl-aniline*	6	2 R salt	0
iodo-aniline	0	benzidine sulfone	
m-iodo-aniline*	0	mono-sulfonic acid	0
p-iodo-aniline*	0	benzidine sulfone	
m-nitro-aniline	0	disulfonic acid	0
p-nitro-aniline*	1	benzidine mono-sulfonic	
p-nitroso-dimethyl-aniline	0	acid 2 H salt	0
anthracene	8	benzidine mono-sulfonic	
dibromo-anthracene	7	acid 2 R salt	0
anthraquinone	2	benzidine mono-sulfonic	
anthraquinone sodium sulfonate	4	acid NH_2R salt	0
anthraquinone monosodium sul-		benzidine trisulfonic acid	3
fonate	1	diaceto-benzidine	0
asparagine	0	*m*-diamino-benzidine	
benzene*	3	hydrochloride	1
p-amino-azobenzene	0	1-iodobenzidine hydrochloride	2
amino-azobenzene hydrochloride	0	2-iodobenzidine hydrochloride	2
diamino-azobenzene hydrochloride	0	4-iodobenzidine hydrochloride	0
dimethyl-amino-azobenzene*	0	benzamidine hydrochloride	7 P
p-dimethyl-amino-azobenzene		hydrobenzoin	4 P
o-carboxylic acid (methyl red)	0	benzoic acid	5 P
amino-azobenzene disulfonic acid	0	*o*-aminobenzoic acid	5 P

[1] The figures 0 to 8 under visibility indicate the intensity of the fluorescence. P stands for distinct phosphorescence. Liquids are indicated by an asterisk *.

TABLE II (*continued*).

Substance.	Visibility.	Substance.	Visibility.
m-aminobenzoic acid	0	ethylene bromide*	2
p-aminobenzoic acid	0	ethylene chloride*	1
o-chlorobenzoic acid	5 P	glutamic acid	7
o-hydroxybenzoic acid (salicylic acid)	8	glutamic acid	2
m-hydroxybenzoic acid	1	glutamic acid	0
p-hydroxybenzoic acid	5 P	glutamic acid hydrochloride	0
1,2,5-homohydroxybenzoic acid	0	glycerol*	0
1,2,4-dihydroxybenzoic acid (β-resorcylic acid)	6	glycine anhydride	3
iodo-hydroxybenzoic acid	0	glycine anhydride	0
methyl-*o*-hydroxybenzoic acid ester	8	glycylglicine hydrochloride	0
phenyl - *o* - hydroxybenzoic acid ester	6	glycylglicine	5
sodium-*o*-hydroxybenzoate	3	glycine ester hydrochloride	1
o-iodobenzoic acid	4	glycine ester hydrochloride	0
o- and *p*-iodobenzoic acid	3	glycine ethyl ester hydrochloride	0
iodosobenzoic acid	0	phenyl-glycine	0
o-nitrobenzoic acid	0	dibromo-guaiacol	5
p-nitrobenzoic acid	0	dibromo-*o*-guaiacol potassium sulfonate	0
1,3,5-dinitrobenzoic acid	2	iodoguaiacol sodium sulfonate	0
p-sulfone amine benzoic acid	6	hexamethylene - etramine tri-guaiacol	5 P
sodium benzoate	5	H acid	1
benzaldehyde*	0	dichlorohydrin*	1
p-amino-benzaldehyde	0	hydroquinone	4
hydroxy-benzaldehyde	0	hydroxy-hydroquinone	0
1,2,4-dihydroxy-benzaldehyde (β-resorcyl-aldehyde)	2	dibromo-thymoquinone	0
1,2 - hydroxy - 5 - bromo - benzal-dehyde	8	iodoform	0
bromal hydrate	0	leucine	0
bromobutyril bromide*	1	leucine 60–100	0
camphor	4	leucine 100–130	0
calcium camphor sulfonate	2	leucine 130–150	0
carbon tetrachloride*	3	residue from leucine purification	1
chloroform*	2	mercury ethyl	0
cholesterol	0	methyl alcohol*	0
cinchonidine	4	naphthalene	4
isocinnoline*	3	naphthylene-1,2-diamine	1
creosol*	2	naphthylene-1,2-diamine hydro-chloride	0
o-cresol*	0	naphthylene-1,5-diamine	0
m-cresol*	0	naphthalene boric acid	0
p-cresol	2	bromo-naphthalene*	5
tricresol *	1	α-methyl-naphthalene*	7
cumene	0	β-methyl-naphthalene*	5
cyanacetic acid	0	1,5-dinitro-naphthalene	0
elaidic acid	0	1,8-dinitro-naphthalene	0
ethyl alcohol*	0	α-naphthalene sulfochloride	2
ethylamine hydro-iodide	0	β-naphthalene sulfochloride	1
		α-naphthalene sulfonic acid	5
		β-naphthalene sulfonic acid	6
		β-naphthalene sodium sulfonate	6

TABLE II (*continued*).

Substance.	Visibility.
β-naphthylene sodium sulfonate (Witt method)	7
naphthalene disulfonic acid	5
naphthalene calcium disulfonate	5
1,8,3,6-dihydroxy-naphthalene sodium disulfonate (chromotropic acid chromogen-1)	3
naphthalene sodium trisulfonate (crude)	4
α-naphthol	4
β-naphthol	2
β-naphthol	0
1,4-α-naphthol monosulfonic acid (crude) (Neville and Winther's acid)	2
1,5-α-naphthol monosulfonic acid (crude)	1
2,6-β-naphthol ammonium sulfonate	6
1,4,8-α-naphthol disulfonic acid (crude) (Schollkopf's acid)	0
1,3,8-α-naphthol disulfonic acid (crude)	4
β-naphthol disulfonic acid	1
2,6,8-β-naphthol disulfonic acid, G acid (crude)	6
2,3,6-β-naphthol disulfonic acid, R acid	6
2,6,8-β-amino-naphthol sulfonic acid (crude)	4
1,8,3,6-amino-naphthol sodium disulfonate H (crude)	0
1,8,4,6-amino-naphthol sodium disulfonate K (crude)	1
α-naphtho-cinnoline	5
α-naphthonitrile*	4
β-naphthonitrile	6
β-naphthoquinone monosulfonic acid	0
naphtho-resorcinol	0
α-naphthyl salicylic acid	5
α-naphthylamine	4
α-naphthylamine hydrochloride	4
β-naphthylamine	2
β-naphthylamine chloride	3
dimethyl-α-naphthylamine*	6
phenyl-α-naphthylamine	7
phenyl-β-naphthylamine	7
2,7-naphthylamine sulfonic acid (crude) (Delta acid) (F acid)	4
1,5-α-naphthylamine sulfonic acid (crude) (Laurent's acid)	0
2,6-β-naphthylamine sulfonic acid (crude) (Bronner's acid)	4
2,8-β-naphthylamine sulfonic acid (crude)	6
2,3,6-β-naphthylamine disulfonic acid (crude) (amino R acid)	4
2,6,8-β-naphthylamine disulfonic acid (crude) (amino G acid)	6
naphthionic acid	1
hydroxy-naphthionic acid	4
sodium naphthionate	8
α-aceto-naphthalide	4
β-aceto-naphthalide	6
benzoyl-α-naphthalide	4
acenaphthene	6
p-nitro-anisole	0
phenacetine	4
phenacetolin	0
phenanthraquinone	1
phenanthrene	7
phenetole*	1
p-phenetole sulfonate	5 P
dibromo-phenetole-4-sulfonic acid	0
p-isobutyro-phenetidine	0
phenol	4
phenol (in water 72%)*	3
phenol (in water 8%)*	1
m-aminophenol	0
p-aminophenol hydrochloride	4
p-bromophenol sulfonic acid	1
p-dibromophenol sulfonic acid	0
tribromophenol	5
o-chlorophenol sulfonic acid	3
chloro-nitrophenol	0
2,6-dichloro-phenol-4-sulfonic acid	5
p-iodophenol	0
di-iodophenol-4-sulfonic acid	0
di-iodophenol iodide	0
o-nitrophenol	0
p-nitrophenol	0
o-nitrophenol, condensed with HgO	0
o-nitro-chlorophenol condensed with HgO	0
phenolphthalein	0
diphenyl	6
di-iodo-diphenyl	0
diphenyl-iodo-iodide	0

TABLE II (*continued*).

Substance.	Visibility.	Substance.	Visibility
diphenyl carbonate	4 P	bromo-pyrogallol-trimethyl ether	6
diphenylamine	5 P	bromo-pyrogallol-dimethyl sulfonic acid	3
diphenylamine hydrochloride	1	quinine hydrochloride	3
methyl-diphenylamine* (crude)	7	quinine sulfate	2
1-phenyl-3-methyl-5-pyrazolone	0	quinoline*	0
3-phenyl-5-chloropyrazole	4	*o*-hydroxy-quinoline	0
hydroxyphenyl mercury acetate	0	resorcinol	4 P
diamino-diphenyl-thio-urea	0	resorcinol dimethyl ether*	0
p-phenylene-diamine	5	tribromo-resorcinol	0
p-aceto-phenylene-diamine	2	di-iodo-resorcinol	0
phenylene - diamino - azo - *o* - toluidine	0	tri-iodo-resorcinol	0
p-phenylhydrazine sulfonic acid	0	terpine hydrate	0
p-amino-acetophenone	1	theobromine	6 P
cinnamylidene-acetophenone	3	thymol	0
pinene*	0	toluene*	3
α-bromo-propionic acid*	0	*p*-bromotoluene*	2
iodo-propionic acid	1	dinitrotoluene*	0
bromo-propionyl chloride*	0	*o*-nitro-toluene sodium sulfonate	1
pyridine*	0	tyrosine	1
pyridine hydrochloride*	1	tyrosine	0
pyrogallol-dimethyl ether barium sulfonate	3	tyrosine and cystine	0
pyrogallol-trimethyl ether barium sulfonate	3	xylene*	4
bromo-pyrogallol-dimethyl ether	6	*o*-xylene*	3
		m-xylene*	2
		1,3-xylenol-4*	4

TABLE III.[1]

The Visible Fluorescence of Dyes.

Substance.	Visibility.	Substance.	Visibility.
acridine	3	benzo blue 3 B	0
acridine orange	0	4 benzo blue	0
phenyl acridine	6	benzo brown G	0
ethyl red	0	benzo fast blue R	0
alizarine dry	0	benzo fast pink 2 BL	4
aniline blue	1	benzo fast scarlet 4 BS	0
anthracene blue	0	benzo fast yellow 5 GL	0
acid anthracene brown R	0	benzo olive	4
anthracene red	1	benzo purpurin	0
anthracene yellow G	2	benzo purpurin 4 B	0
auramine	5	benzo purpurin 6 B	0
aurantia	0	benzo purpurin 10 B	0
azo blue	3	benzo sky blue	5
azo-eosin	0	bismarck brown	0
benzo-azurine	5	bitter almond oil green	0
benzo-azurine G	1	bordeaux G	0
benzo-azurine 3 G	2	brazilin	0
benzo black blue 5 G	1	brilliant cresyl blue	0

[1] The figures 0 to 8 under visibility indicate the intensity of the fluorescence. No dye fluoresced brightly and none was noticeably phosphorescent.

TABLE III (*continued*).

Substance.	Visibility.	Substance.	Visibility.
carminic acid	0	naphthamine blue BXG	0
quinoline yellow	3	naphthamine blue BXR	0
quinoline yellow spirit	1	naphthamine blue JE	0
quinoline red	0	naphthamine blue 3 R	0
chloro-fuchsin	0	naphthamine blue 3 RE	0
chromogen	4	naphthamine brilliant blue B	0
chrysamine G	0	naphthamine brilliant blue BW	0
chrysoidine	0	naphthamine brilliant blue BWO	0
congo red	0	naphthamine brilliant blue G	0
coralline	0	naphthamine brown 8 B	0
coralline alcohol soluble	0	naphthamine brown GX	0
coralline water soluble	0	naphthamine brown 4 G extra	0
crocein	1	naphthamine brown H	0
crystal violet	0	naphthamine brown RB	0
cyanine	0	naphthamine deep black HW	0
diamond black	1	naphthamine direct black C	0
eosin w.	1	naphthamine direct black EK	0
erythrosine	0	naphthamine direct black O	0
fluorescein	0	naphthamine direct black RWK	0
fuchsin f. bac.	0	naphthamine direct brown 2 R	0
gentian violet BP	0	naphthamine fast black KS	0
hematoxylin	0	naphthamine fast black SDE	0
hemalaun dry	0	naphthamine fast black SE	0
hematein	0	naphthamine fast black VE	0
indigo carmine	0	naphthamine fast bordeaux BG	0
iodo-methylene blue	0	naphthamine fast scarlet B	0
iodo-eosine	0	naphthamine fast scarlet R	0
iodine green	0	naphthamine green A	0
malachite green	0	naphthamine green AB	0
methylene blue	0	naphthamine green AG	0
methylene blue 2 B extra	0	naphthamine green B	0
methyl eosine	0	naphthamine green TE	0
methyl orange	0	naphthamine orange 2 R	0
methyl violet	0	naphthamine red H	0
naphthalene red	0	naphthamine scarlet B	0
naphthamine black BN	0	naphthamine violet BE	0
naphthamine black BNN	0	naphthamine violet N	0
naphthamine black GE	0	1,2-naphthoquinone-4,6-sodium disulfonate	0
naphthamine black H	3		
naphthamine black HRE	3	1,2-naphthoquinone-4-sodium sulfonate	0
naphthamine black 2 RE	0		
naphthamine black 3 RE	0	naphthol yellow S	0
naphthamine black 4 RE	0	naphthol green	0
naphthamine black RGE	3	naphthol orange	0
naphthamine blue	0	naphthylamine black 10 B	0
naphthamine blue 7 B	0	naphthylamine black BOO	0
naphthamine blue 12 B	0	naphthylamine black NR	1
naphthamine blue BE	0	neutral red	0
naphthamine blue 2 BL	0	nigrosine base	0
naphthamine blue 2 BX	0	nile blue sulfate	0

TABLE III (*continued*).

Substance.	Visibility.	Substance.	Visibility
orange G	0	rubin	0
orcein	0	safranine (alcohol)	0
phloxin red	0	scarlet red	0
phosphin 3 R	0	solid green	0
ponceau PR	0	sudan III	0
pyronine	0	tropaeolin	0
rapid filter yellow	0	tropaeolin-*o*-resorcine yellow	0
rapid filter green I	0	trypan blue	2
resorcine fuchsine	0	trypan red	1
rosanilin acetate	0	uranin (fluorescent)	2
rose bengale	0		

Summary.

An extended search for a substance which might be available for application in animal experiment (relatively soluble), and at the same time capable of emitting fluorescent rays in the mid-ultra-violet region of the spectrum under the influence of the X-ray, has revealed only sodium bromide as possessing these qualities. Many organic chemical compounds fluoresce brightly in the visible region of the spectrum and a moderate number of them give fluorescence which is capable of blackening the photographic plate.

It has been shown that there are solids, liquids, gases and certain solutions which fluoresce. The phenomenon is not limited to any physical state. The nature of the fluorescence excited in any material, both as to intensity and quality is independent of the quality of the exciting X-rays and dependent on their energy alone.

I wish to express my appreciation to Dr. Paul Lewis for the very considerable interest which he has taken in this problem.

PHILADELPHIA, PENNA.

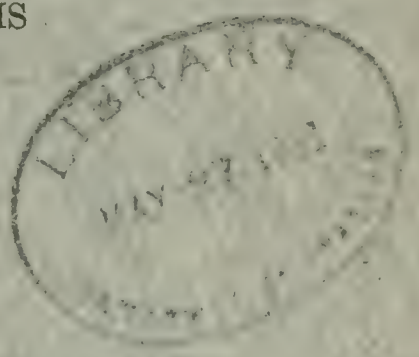
UNIVERSITY OF PENNSYLVANIA

SIXTEENTH REPORT

OF THE

HENRY PHIPPS INSTITUTE

FOR THE STUDY, TREATMENT AND
PREVENTION OF TUBERCULOSIS



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* The Eagleville Sanatorium Association has the use of the hospital wards for the care of advanced cases of tuberculosis. The arrangement is made under conditions that provide for supervision by the Henry Phipps Institute, and opportunity of the study of cases in connection with research problems.

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19. Aids to Basal Metabolic Rate Determinations. By H. S. Newcomer.

20. A New Optical Instrument for the Determination of Hemoglobin. By H. S. Newcomer.

21. A Sulfonated Naphthylarsinic Acid. By A. Elizabeth Hill and A. K. Balls

22. The Early Development of the Corneal Tubercle. (A Study in Slit Lamp Microscopy.) By Drs. Bertha T. Haessler and F. Herbert Haessler.

23. Dorset's Egg Medium and Modifications. By Casper G. Burn.

24. Studies on the Bacterial Flora of the Sputum from Cases of Tuberculosis and Other Chronic Respiratory Infections. By Casper G. Burn.

25. Specific Purification of Anti-Tuberculosis Serum. By Joseph D. Aronson.

Oration in Medicine

Delivered at the 156th Annual Meeting of the Medical Society of New Jersey, at Spring Lake, June 22, 1922.

Tuberculosis Campaign and Some of Its Accomplishments

By HENRY R. M. LANDIS, M. D

PHILADELPHIA, PA.

The modern crusade against tuberculosis was launched nearly two decades ago. It may not be amiss, therefore, to briefly review the situation prior to this and epitomize what has been accomplished subsequently.

Medical history abounds in instances in which a pioneer worker has pleaded in vain with his own generation for the acceptance of a truth. Too often his efforts have been wasted and years later some student of the past discovers that what is a universally accepted fact was at one time advocated in vain. Tuberculosis offers many examples of this. The modern conception of the management of the disease which is now almost universally accepted was known and proclaimed in part or in whole by a few many, many years ago. Sydenham in the 18th century had the germ of the idea; McCormack (1830) followed very closely the present ideas; William A. McDowell (1843) strongly disapproved of the common practice of blood-letting and purging and advocated four meals a day, outdoor life and graduated exercises; Brehmer, frequently referred to as the father of the modern sanatorium treatment, began his work in 1859; Trudeau, the pioneer in this country in sanatorium treatment (1884), waited many years before anything like a general acceptance of his ideas prevailed. Finally, as a matter of local interest, I might mention the case of Dr. Joseph Parrish of Philadelphia. He belonged to a prominent family of the Quaker Sect, was an abolitionist and one of the founders of the famous "under-ground railroad" which aided the escape of slaves prior to the Civil War. As a young man, in the early years of the last century, he contracted tuberculosis; feeling that he could cure himself, he spent a year in the open in the pine woods of New Jersey, making a complete recovery. Many of his colleagues doubted his having had the disease. After his death many years later an autopsy showed a large area in one lung which had completely healed.

Knowing that so many physicians scattered through the past had a fairly accurate conception of the problem, one naturally asks: "Why was this knowledge so long in being acquired by all of the profession?" The answer lies in the fact that an educational propaganda was unknown. It was only as the result of a prolonged and intensive educational campaign that we have traveled along the road as far as we have.

In spite of the fact that tuberculosis is and always has been one of the leading causes of death in every community, medical students until comparatively recently were being graduated with no knowledge whatever of the disease. I began the study of medicine in 1894 and during the three years I was a student I never heard a single lecture on the subject of tuberculosis nor was I shown a single example of the disease in the clinic. Fortunately or unfortunately, for myself, I had to acquire the disease some three years after graduation, to find out anything about it. And I may

add most of the men who have evinced any interest in the disease have been at one time one of its victims.

The pioneer work of the few who struggled for years received an impetus forward by the discovery of the tubercle bacillus. In the last ten years of the last century interest in the subject became more general and agencies for combating the disease slowly increased. Next to the foundation of the Adirondack Cottage Sanatorium by Trudeau in 1884 the next most notable advance was the foundation of the Phipps Institute in 1903, by Mr. Henry Phipps under the directorship of Dr. Lawrence F. Flick. As the latter said in dedicating his book to Mr. Phipps, this was the first large venture of the kind and was of the greatest value, if for no other reason than the publicity it gave to the subject. Several years prior to the foundation of the Phipps Institute, the idea of forming a national body for combating tuberculosis had been in the minds of some.

Finally in Philadelphia in 1904, following a preliminary conference in Baltimore in 1903, the National Tuberculosis Association came into being as the result of a meeting of distinguished tuberculosis workers from all over the country. The foundation of this Association was in many respects the most notable public health achievement ever undertaken in this country. It is the first organization which concentrated all of the available medical ability on a single disease.

Furthermore, the work of this Association has brought about a realization of the fact that tuberculosis is, more than any other disease, a social problem and that nearly everything that relates to the health of the public is included in the battle against it,—better housing, a knowledge of dietetics, occupation problems, etc. It, therefore, has been the source from which many other public health movements have been shaped.

I am not going to weary you with a recital of the number of tuberculosis agencies of one sort or another that were in existence two decades ago and the number that exists today. Suffice it to say the National Tuberculosis Association has extended its activities into every State, even more, there are relatively few communities of any size throughout the country which are not influenced to some degree by this great educational movement.

What effect these fifteen or twenty years have had on the general health is not easy to measure. There is one thing, however, that serves to illustrate beautifully the effect of educational work intensively and persistently carried out. I speak of the almost universal practice at the present time, of sleeping in well-ventilated bed-rooms or even in outside sleeping rooms. The generation before us, and possibly a good many of those present, slept, as children, in a room with the windows closed and not infrequently a gas jet burning. Practically speaking, this has ceased to be. Open air is no longer feared and the knowledge of its health-giving advantages is recognized. In fact, many modern houses are so designed as to provide for an outside sleeping porch. This innovation furnishes another example of the influence of an educational campaign directed primarily against one disease and later adopted for others. The recognition that a disease which prevailing opinion associated with exposure could be benefited by an abundance of fresh air gradually led to its adoption in the management of other conditions, notably pneumonia.

Furthermore, it has revolutionized the ventilation of hospital wards. While there is still much to be devised, overheated and badly ventilated wards are becoming less and less common.

At the time the National Association was formed the almost universal opinion in regard to the treatment of tuberculosis was that a suitable climate was essential. Whether the patient could pay for a sojourn in one of the health resorts or not, this was recommended as the one means of being cured. While it is true that there were a few physicians who advocated carrying out the treatment in the locality in which the patient was living, this view was frowned down upon and home treatment was by the majority considered rank heresy. The possibilities of home treatment, nay the necessity for it in the great majority of cases, have been brought about by the crusade conducted by the National Association.

In regard to your own State, the first organization for the prevention of tuberculosis was the Anti-Tuberculosis Committee of the Oranges in 1904.

The New Jersey Association for the Prevention and Relief of Tuberculosis was established in 1906. In 1913 it was

reorganized. By this time local organizations had been formed in most of the large cities of the State so that at present it is really a league of local societies. In addition, since 1913, a large number of local societies have come into being in territory not previously covered. There are at present 38 local associations, definitely affiliated with the league and most of them have full-time executives.

New Jersey is to be commended as being among the first States to recognize the necessity for local county hospitals. Under the county hospital laws of 1910 and 1912, the league has developed 9 county hospitals and 4 city sanatoria. Until these county hospitals could be provided, several of the counties in the northern part of the State sent their patients to the White Haven Sanatorium in White Haven, Pa. Many of these patients have been under my care.

In addition to the county hospitals there is a State sanatorium and one private sanatorium furnishing in all 1,688 beds. Furthermore, there are 18 clinics and dispensaries, 5 camps, 2 preventoria and 40 open-air classes. Eighty-four towns and cities have public health nursing service, the number of nurses being considerably in excess of the number of towns.

The Tuberculosis League has made its influence felt in other directions. Through its legislative activity there have resulted a law directed towards the prevention of public spitting; the abolition of the roler towel and public drinking cup; better housing laws; improved factory conditions and the compulsory reporting of tuberculosis.

Granting that the death rate from tuberculosis has been gradually falling for the last half century, it can hardly be denied that all of the activities just cited have had an influence. In 1906, when the State Association was organized, the mortality was 196 per 100,000; in 1920 it had fallen to 114.

This brief review of the activities in your State with its provision for those actually ill and the enactment of laws designed to improve the general health conditions is representative of most of the country at large.

The record in your State is one you may well be proud of but there remains still much to be done if tuberculosis is to be reduced to a negligible minimum. I might mention several of the most important things to be accomplished.

1. What we understand today as Internal Medicine was made possible by the epoch-making work of Laennec. And when one recalls that this was accomplished through his painstaking study of tuberculosis, it is strange that the causative factors, the pathology, the symptomatology and the physical findings of this disease are so imperfectly understood by many practicing physicians.

Granting that the disease lacks the clinical interest of many other conditions, it must be apparent to every one that a disease which is so common in all localities and one that is responsible for a third of all the deaths between the ages of 25 and 45, must be understood in all its manifestations if the physician is to serve his community efficiently.

In the main the diagnosis is not difficult if one is constantly alert and keeps in mind the frequency of the disease and the fact that it apes many other conditions. To belittle the importance of an hemoptysis or a pleurisy or to treat a patient for bronchitis for months is inexcusable. Every patient allowed to drift along until he who runs may read the signs is a lasting reproach to the doctor.

I believe, not because I am identified with tuberculosis work, but because of my interest in preventive medicine, that every practicing physician should be identified with his local tuberculosis organization. If this were done, diagnostic methods would be improved and the health of every community would be improved because the tuberculosis problem touches every phase of the community's life.

II. It may surprise you to learn that this State has a very large Negro population. During the past decade there has been an enormous migration of the Negroes North and West. In considering the Negro problem it is generally regarded as one that concerns the South alone. More and more, however, it is one that many Northern States face. Pennsylvania with 284,000 in a total population of 8,720,017 (3.3%) has the largest number of Negroes of any State outside of the South. The major portion of Negroes in Pennsylvania is in the City of Philadelphia with an estimated population of 150,000. It is to be noted, however, that. New Jersey has 117,000 in a total population of 3,155,900 (3.7%). Proportionately this is larger than that

of Pennsylvania and it is also to be remembered that New Jersey is about one-fifth the size of Pennsylvania.

Only recently it was brought to my attention that the City of Camden has a Negro population of 14,050.

In view of the high mortality from tuberculosis among the Negroes and the corresponding high mortality rate it is obvious that any tuberculosis program which fails to make provision for this phase of the problem is inefficient. It is not a question of sentiment but one of necessity. It must be remembered that these people are constantly being brought into close contact with the whites in the capacity of domestic servants, laundresses, etc. Then, too, it is an important economic question.

For eight years we have been dealing with this problem at the Phipps Iinstitute. Prior to that time we had very few Negro patients although situated in the midst of a large Negro population. As we failed with the ordinary means, we determined to try the experiment of using Negro nurses and physicians. The practicability of this has been fully established. The size of the clinic has steady increased and the scope of the work has been greatly broadened. Starting with one nurse and one physician, we now have attached to the Institute eight colored nurses and four colored physicians. There can be no doubt but that this is the solution of the problem and any community which has a large Negro population would do well to put it in force.

The prevailing opinion is that tuberculosis in the Negro is incurable and that little can be done for them. Two recent reports are, therefore, of interest. The Metropolitan Life Insurance Company has shown that the death rate from tuberculosis among their policyholders (numbering 1,600,000) has dropped from 17.5 per 1,000 in 1911 to 13.2 per 1,000 in 1921. Dr. Carter of Virginia, who is in charge of a Negro Sanatorium, reports that the Negro is just as amenable to recovery in the early stages of the disease as the whites, providing he is given proper treatment.

III. Members of the profession in New Jersey have another important duty to perform in the tuberculosis campaign. There are a large number of manufacturing interests—several of which entail a distinct industrial hazard. The City of Trenton is the center of the pottery industry in this country and those living in or about Trenton know of the great frequency of pulmonary affections among potters. Within recent years a great deal of attention has been given to the subject of pneumoconiosis—a condition which results from exposure to inorganic dust. At the present time there is much to learn about this condition, particularly its relationship to pulmonary tuberculosis. The prevailing opinion is that the real hazard of the dust is the tendency of the worker to eventually become tuberculous. Whether this is true or not there is no doubt that constant exposure to inorganic dust does produce marked fibrosis of the lungs and does eventually incapacitate the worker whether he becomes tuberculous or not.

My interest in the subject began some years ago.. The Potters' Union has for some years sent those of its members who had, or were thought to have, tuberculosis to the White Haven Sanatorium. In a paper I recently read on the subject there had been treated up to date some 90 cases. A thorough study of these dusty trades is needed for several reasons. First to determine whether it really does predispose the worker to infection with the tubercle bacillus and, second, to devise means to eliminate the danger from the inhalation of dust. And at the same time the danger of leading poisoning to which some of the workers are exposed should receive attention.

Aside from the question of the health of the worker the question is of economic importance. The crippling effect that may result to an industry is illustrated by the experience of the granite cutting trade in Barre, Vermont. The high incidence of pulmonary affections among this group became so great that the occupation received a bad name. As a result it was difficult to induce men to enter the trade. This became so serious that a thorough study of the problems involved was undertaken—the expense being shared by the National Tuberculosis Association, the employers and the workers themselves. As a result of this study many innovations were introduced to eliminate the dust. Had this not been done the entire industry would probably have been ruined. While it is true that the danger is not quite so great in the potteries, it is true that far too many men have their wage earning careers

shortened because of hazards peculiar to their trade and which could be removed entirely or greatly mitigated.

The State Medical Society could do no greater service than that of using its influence in behalf of studies of this sort

Another of my earlier experiences with industry in its relationship to tuberculosis was obtained also in this State. Some five or six years ago one of the northern counties of the State sent to the White Haven Sanatorium, in the course of a few months, a group of young women all of whom gave as their occupation that of cigarmaker. As you know this trade has a very high incidence of tuberculosis, in fact one of the highest, and this is usually ascribed to the injurious effects of tobacco dust. Personally, I had always doubted this, believing that organic dust had no effect on the lungs. I, therefore, determined to visit the homes of these women and also their working places. With one or two exceptions, they came from a small group of towns of recent growth. The hygienic conditions were vile and the living habits of the families of these patients were worse. In addition there was a low rate. The other side of the picture was the factory. This was all it should be—modern, well lighted and ventilated. Furthermore, there was no such thing as tobacco dust for the obvious reason that the manufacture of cigars from the beginning of the process to the very end requires that the tobacco leaves be moist and pliable. Nor is there any waste as the stems, loose ends, etc., are all sold and enter into the manufacture of snuff or smoking tobacco.

Here then we have two types of industry—one, the pottery, paying large wages but entailing a distinct hazard in the working place itself; the other poorly paid and entailing **per se** no hazard whatever.

The former requires certain definite preventive measures in the factory; the latter educational work in the matter of public and private hygiene and more important still—a health budget for each community sufficient to correct and enforce health standards. In several of the towns in which the cigarmakers worked there was no health organization whatever. The wage question is one that is entirely outside the scope of the physician and sanatarian except insofar as they can show the effects of low wages on living conditions.

There are certain other problems connected with the campaign against tuberculosis which I might touch upon but time forbids. I hope I have given you enough, however, to show how intricate the problem is and how it reaches out in all directions. Every physician in every community throughout this State is directly concerned.

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Meeting of National Tuberculosis Association

THE CLINIC FOR NEGROES AT THE HENRY PHIPPS INSTITUTE

By H. R. M. Landis, M.D.

Philadelphia

In the earlier period of the Phipps Institute's work, it was found impossible to do satisfactory work with the Negroes. Those who came to the clinic, more or less by accident, could seldom be induced to persist in their attendance, and no considerable progress could be made with them as individuals. Moreover, the educational effort, which at the time served to bring increasing numbers of whites to the clinic, had no perceptible influence in increasing the interest of the colored people in their health.

It seemed likely that this situation could be changed by adopting the principle of operating through the medium of selected colored workers. The Whittier Center, an agency which had long worked for the welfare of the Negroes, was induced to employ a colored nurse to work as a member of the staff of the Institute. Mrs. Tyler was engaged in 1914. She was taught the methods employed by the white field nurses and instructed to go among the colored people and induce any with whom she might make contact to come to the clinic, in so far as there was reason to think that they might be suffering from lung trouble.

Mrs. Tyler's work, from the beginning, had an appreciable influence. Alone it did not seem to offer a complete solution of the difficulty. The situation was again greatly improved when a capable colored physician, Dr. Minton, became associated with the clinic, in 1915.

Dr. Minton's work has been of high quality, and after several years there is no reason to feel that, allowing for the matter of intelligence (and in this the Negro does not suffer particularly when compared with the white patients of the dispensary), work with the Negroes is in any way less successful than with the whites.

In the interval, the nursing service has been supplied in various ways. The Whittier Center continued for some years to support a worker. Later, the Pennsylvania Tuberculosis Society supplied one. Later still, the Philadelphia Health Council has supplied one. At times there have been two nurses on the service, at other times only one. The past service of Mrs. Tyler has been mentioned. Miss Turner was also associated with this clinic at one time. At present the organization of the Negro Clinic is as follows:

Dr. Landis in charge — Paid by the Phipps Institute and by the Department of Health of the State of Pennsylvania.

Dr. Henry Minton (colored), since 1915 — Paid by the State Department of Health.

Dr. Frank Boston (colored), 1921 — Paid by the State Department of Health.

Dr. G. A. Saunders (colored), 1921 — Paid by the State Department of Health.

Miss Johnson (colored), since 1915 — Field nurse, paid by the Philadelphia Health Council.

Miss Ernst (colored), since Nov., 1920 — Field nurse, paid by Whittier Center.

Treatment for syphilis, whenever encountered, is also afforded by Dr. Baird Stuart of the Phipps Institute staff.

The work of the clinic for 1920 is summarized as follows:

MISS JOHNSON'S YEARLY REPORT

New patients		266
Unfinished cases	37	
Positive tuberculosis	116	
Positive and Luetic	4	
Non-tuberculosis	52	
Non-tuberculosis and Luetic	22	
Indefinite	25	
Indefinite and Luetic	10	
Patients' visits to the dispensary		2099
Patients sent to hospitals		34
Patients referred to sanatorium		12
Cases closed		69
Death	19	
Moved	20	
Lack of coöperation	25	
Referred to private physicians	5	
Nurse's visits to the homes		1126

MISS ERNST'S REPORT (2 MONTHS)

WHITE PATIENTS

	Male	*Female*	*Children*
New:	10	1	9
Old:	17	11	14
	—	—	—

Total 62

	Total
Pre-natal patients—3 old, 15 new	18
Babies — 4 old, 11 new	15
Pre-school age — 2 old, 5 new	7
Gynecological Clinic	4
Patients' visits to clinic	190
Nurse's visits to homes	68
G. U. Patients	44
Tbc	1

Gynecological Patients. 2
Post-natal patients. 14
Pre-natal patients. 27
Wassermanns. 34

The following table shows the number of colored patients from the opening of the Institute up to the present:

NEW COLORED PATIENTS

1904–1921

	Male	*Female*	*Adult*	*Child*	*Total*	
1904. . . .	32	15	40	7	47	Mostly ward patients.
1905. . . .	18	10	26	2	28	
1906. . . .	46	30	55	21	76	
1907. . . .	36	22	50	7	57	
1908. . . .	33	16	43	6	49	
1909. . . .	36	31	57	10	67	
1910. . . .	20	17	32	5	37	
1911. . . .	28	20	37	11	48	
1912. . . .	23	22	41	4	45	
1913. . . .	34	23	49	8	57	
1914. . . .	66	55	106	15	121	Colored nurse began work.
1915. . . .	56	61	No record	No record	117	
1916. . . .	70	71	" "	" "	141	
1917. . . .	73	69	" "	" "	142	
1918. . . .	70	70	" "	" "	140	
1919. . . .	77	113	" "	" "	190	
1920. . . .	129	116	" "	" "	245	
Total. . . .					1487	
1921 (Feb., Mar., Apr.) New cases. . . .					114	

Colored patients receiving treatment in 1919:
833 individual patients.
1047 treatments given to 833 patients.
Colored patients receiving treatment in 1920:
1358 individual patients.
2099 treatments given to 1358 patients.

It will be noted that in 1914, the number was more than double as a result of the educational efforts of the colored nurse for about six months; and later by the addition of another colored nurse.

During the years 1916-1918, the number stayed at about the same level. This can probably be credited to the unusual prosperity due to war activities. With the closing of many of the war industries, the number of patients noticebly increased, — (190 in 1919; 245 in 1920). For the first three months of the present fiscal year, the number of new patients has been 114. If this ratio continues, the number for the year will approximate 450. The figures given here relate to the general tuberculosis dispensary. In November, 1920, an additional colored nurse was

secured. She has charge of the syphilis clinics and of the colored pre- and post-natal clinics.

About 30 per cent. of the Negro patients visiting this dispensary have syphilis, as shown by a Four Plus Wassermann. The result is to show that many need specific treatment. These clinics are held on Monday afternoons for women and children, and on Thursday night for men. The result of putting a Negro nurse at work among the Negroes is again well shown by the development of the pre- and post-natal work. The following table shows the development of this work:

NEGRO PATIENTS IN SYPHILIS CLINIC
(Report for 4½ months)

	Male	*Female*	*Children*
New:	24	29	7
Old:	63	65	18
	87	94	25

Total	206
Pre-natal	28
Babies	37
Pre-school age	10
Number of visits to homes	258

Starting with nothing, she now has 28 pre-natal and 37 post-natal patients under observation.

Another Negro activity of considerable interest is the establishment of two classes for under-nourished children. These classes are conducted by a colored nurse and a colored physician. Although conducted under the auspices of the Philadelphia Health Council, they are the result of the demonstration class conducted by the Institute a year ago.

It might be added that since the first colored nurse was engaged in 1914, seven are now employed in public health work among the Negroes. The Visiting Nurse Association has two, the City two, the Philadelphia Health Council two (one of whom is assigned to the Institute), and another is shortly to be added; and the Whittier Center has one, also assigned to the Institute.

Two additional Negro physicians have recently been added to the staff of the Institute.

The problem of dealing with the Negro is becoming a serious one for us. The work has developed to such an extent that it threatens to swamp us. We have under consideration the renting of a building near by, and transferring to it all of the Negro activities. This plan, however, will have to be approached carefully, in order to avoid the suspicion of segregation. A suggestion as to this plan has already aroused suspicion. In order to complete the experiment, however, this would seem to be advisable. The feasibility of utilizing Negro physicians and nurses has been definitely proved. What they can do, if placed more completely on their own resources, remains to be seen.

SUMMARY

As the matter stands at present, there is operating at the Institute a clinic held by and for Negroes (with expert white guidance and supervision) which is doing health work on the most modern lines and with a degree of competency which compares favorably with that of the average clinic for whites of the same kind. It is the only venture of the kind in this vicinity, and we know of no other like it anywhere. The general method of approach is that followed by most successful effort in connection with the Negro (as good a quality of endeavor by the Negroes themselves as can be secured with careful, sympathetic direction and supervision by whites).

The importance of the problem may be emphasized. Philadelphia has to-day upward of 125,000 Negro residents. They are only partially segregated. As servants, they go most intimately into many homes of the whites, and are a constant source of possible infection there. Vienna to-day, under conditions bordering on actual starvation, has a tuberculosis death rate of just about 500 per 100,000 living. Among the Negroes of Philadelphia in 1919 the death rate, on the same basis, was 477. Viewed in this light, the problem is truly appalling.

All concerned, the Whittier Center, the Pennsylvania Society, the Philadelphia Health Council, and those who have supported the Phipps Institute, have reason to congratulate themeselves on the success of this effort to date.

For the future it may be possible, with combined and additional support, to predict the following accomplishments:

The system of work (active, well trained and well supported colored workers, supervised by and associated with the most competent whites) may be extended to cover the problem in this city.

Certain parts of the work may eventually be transferred to the city or State Department of Health for operation.

Facilities may be afforded for the training of additional colored workers, physicians and nurses.

The system may come to be regarded as a model by those interested in health problems in other places having a concentrated Negro population.

The result may be to reduce the present appalling tuberculosis mortality among the Negroes to approximately the normal level for the community.

It would appear that all organized effort to accomplish the latter objective should be considered, at present, to be also an experimental check on the current methods of anti-tuberculosis work of similar practicability and value to the so-called Framingham experiment, which is at present attracting so much attention.

Reprinted from the Virginia Medical Monthly, January, 1923.

The Tuberculosis Problem and The Negro.*

By H. R. M. LANDIS, M. D., Philadelphia, Pa.

Among the serious problems facing us today is that of the Negro. His social, economic, and political status has been debated pro and con for some years. Relatively little attention, however, has been devoted to his physical well being. Those interested in the broad subject of public health have viewed with considerable apprehension, however, the great prevalence in this race of the venereal diseases and the alarmingly high death rate from tuberculosis.

In the North especially there is an indifference to the subject. Many people have no realization that our Northern Cities have a Negro problem. This seems strange in view of the fact that many of our Northern cities contain an enormous number of Negroes.

The dissemination of the Negro population throughout the country has been pointed out in a recent article in the *Literary Digest* (February 25, 1922). Judge A. S. Van de Greaff, of Alabama, states that the Negroes are migrating northward and westward in large numbers. Indeed, their migration is so large and so steady that we can almost certainly look forward to the day when there will be no more "black counties" in the Gulf States.

The following statistical analysis of the Negro population is significant. There are today more Negroes in Cincinnati than in Louisville; more in the border states of the North than in the border states of the South. "On the Southern side there has been a steady decline, at first only relative, but later absolute, until in Kentucky there are now fewer Negroes than in 1860, and the black percentage of its population has become less than that for the United States as a whole; until also, as is even more significant, the last census has shown the loss of black population in all the four contiguous subjacent states,—Tennessee, Alabama, Mississippi and Louisiana. This radical change of trend—this decisive turn toward uniformity in the redistribution of the Negroes between North and South under the conditions of freedom, is thus shown to have already operated over wide areas, and it is now being extended over the whole country. From the returns of the census of 1920 we find in the Northern group 1,236,000 Negroes, showing a decimal gain of 380,000 or 44 per cent.; and in the Southern 1,917,000, showing a gain of 26,000 or less than 1½ per cent. And if we again extend the comparison back to 1860, as the beginning of the new dispensation, we have in the Northern area an increase of 1,002,000 Negroes or 448 per cent., against one of 538,000 or 60 per cent. only, in the Southern."

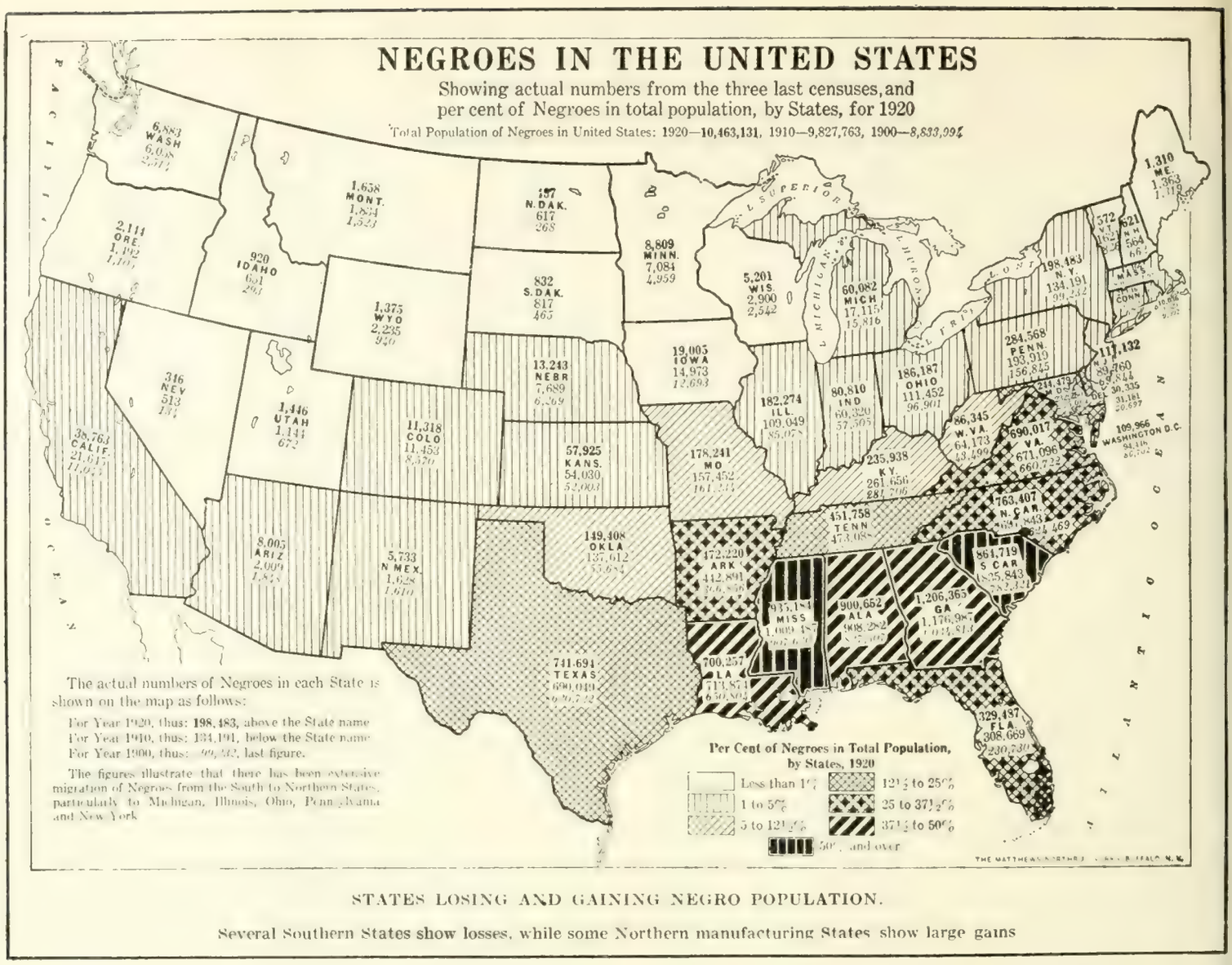
The census of 1920 shows that there were 10,463,131 Negroes in the country at large; in 1910 there were 9,827,763; and in 1900, 8,833,-944.

The appended map (Fig. 1) shows at a glance the distribution of this race. It is interesting to note that in 1896 Frederick L. Hoffman published a study entitled "Race Traits and Tendencies of the American Negro." He summarizes the chapter devoted to the various diseases to which the Negro is liable as follows: "The general conclusion is that the Negro is subject to a higher mortality at all ages, but especially so at the early age periods. This is largely the result of an inordinate mortality from constitutional and respiratory diseases. Moreover, the mortality from these diseases is on the increase among the colored, and on the decrease among the whites. *In consequence, the natural increase in the colored population will be less from decade to decade, and in the end a decrease must take place.** It is sufficient to know that in the struggle for race supremacy the black race is not holding its own; and this fact once recognized, all danger from a possible numerical supremacy of the race vanishes. *Its extreme liability to consumption alone would suffice to seal its fate as a race.** That alone would suffice to make impossible numerical supremacy in the Southern States. 'Sufferers from phthisis,' writes Mr. Haycraft, 'are prone to other diseases such as pulmonary and bronchial attacks, so that over and above the vulnerability to the one form of microbe, they are to be looked upon as unsuited not only for the battle of life but especially for parentage and for the multiplications of the condition for which they themselves suffer.'"

In spite of this pessimistic opinion, a study of the map already referred to shows the great increase in the Northern and Western States

*Read by invitation before the Sixty-third annual meeting of the Medical Society of Virginia in Norfolk, October 31 November 3, 1922.

*Italics are mine


NEGROES IN THE UNITED STATES
Showing actual numbers from the three last censuses, and per cent of Negroes in total population, by States, for 1920
Total Population of Negroes in United States: 1920—10,463,131, 1910—9,827,763, 1900—8,833,994
The actual numbers of Negroes in each State is shown on the map as follows:
For Year 1920, thus: 198,483, above the State name
For Year 1910, thus: 134,191, below the State name
For Year 1900, thus: 99,232, last figure.
The figures illustrate that there has been extensive migration of Negroes from the South to Northern States, particularly to Michigan, Illinois, Ohio, Pennsylvania and New York
Per Cent of Negroes in Total Population, by States, 1920
Less than 1%
1 to 5%
5 to 12½%
12½ to 25%
25 to 37½%
37½ to 50%
50% and over

STATES LOSING AND GAINING NEGRO POPULATION.

Several Southern States show losses, while some Northern manufacturing States show large gains

and in spite of the migration from the Southern States, many of them show an increase in 1920 over that of 1910.

Pennsylvania leads all states other than the Southern, in the size of its Negro population. There are probably several reasons for this: (1) The large Quaker population with its anti-slavery views early led to the settlement of Negroes in the state; (2) Philadelphia, with an estimated Negro population of 150,000 is the first large city encountered on the way North; (3) the multiplicity of industrial plants in the state offers a ready field for employment.

The following extract is made from the Report of Dr. M. P. Horwood who made a survey of the tuberculosis situation in Philadelphia during the past summer:

That Philadelphia is confronted with a serious Negro problem from the standpoint of tuberculosis and the general public health is evident from the following table:

SHOWING THE COMPOSITION OF THE POPULATION OF SEVEN LARGE CITIES IN THE UNITED STATES IN 1920, WITH PARTICULAR REFERENCE TO THE NEGRO COMPONENT.

CITY	TOTAL POPULATION	NEGROES	PER CENT NEGROES
Philadelphia	1,823,779	134,229	7.
New York City	5,620,048	152,467	2.
Chicago	2,701,705	109,458	4.1
Detroit	993,678	40,838	4.
Cleveland	796,841	34,451	4.
Boston	748,060	16,350	2.
Baltimore	753,826	108,322	14.
U. S.	105,710,620	10,463,131	9.

An analysis of the 1920 Federal Census figures for the population of seven of the largest cities in the United States shows that in only one other city, namely New York, is the Negro population greater than that of Philadelphia. The number of Negroes in Philadelphia would in themselves make a large city. When the percentage of Negroes to the total population is considered, however, it is found that the concentration of Negroes in Philadelphia is 2.7 times that of New York, so that in reality the Negro problem is much more acute in

Philadelphia. The Negro population of Philadelphia is greater than that in any of the other cities considered in this study including Baltimore, which is generally known as having a large colored population. Of the seven cities whose statistics were analyzed Baltimore alone had a higher concentration of Negroes.

It is also interesting to note that the concentration of Negroes in Philadelphia is almost as great as that found in the entire country. It is indeed unusual to find a northern city with such a distinctly Negro problem. The number of Negroes in Philadelphia was largely increased during the war by migration from the South, in order to fill the numerous vacancies in industry which occurred at that time. That the prevalence of a large Negro population in Philadelphia has materially increased the tuberculosis death rate will be demonstrated more specifically in the analysis of the mortality rates from tuberculosis by color, and by wards. It will be observed that the death rate from tuberculosis among Negroes in Philadelphia is considerably higher than that among the whites, and that most of the wards having a large concentration of Negroes, also show highly mortality rates from tuberculosis.

The same state of affairs is shown in New York City with an estimated Negro population of 168,000.

In 1910 the mortality rate per 100,000 inhabitants was 202 among the white and 617 in the colored population. Both rates, of course, have declined markedly since that time —in fact, have been reduced 52 per cent., or more than one-half—being, respectively in 1921, 97 among the white and 299 among the colored.

It is interesting to note that the decline of 52 per cent. since 1910 in the tuberculosis death rate has been the same for both the colored and the white populations. This well illustrates how important are general conditions—either economic, sanitary or the availability of food supplies—in effecting the development or the reduction of tuberculosis among all classes of citizens. The equal sanitary supervision of all classes of tuberculosis by public health authorities, and the general educational measures, have produced a rate of improvement among the colored equal to that among the remainder of the population, though naturally starting from and remaining at different levels. (*Bulletin of the New York Tuberculosis Association*, Sept. 1922, Vol. III., No. 4, p. 11.)

As has already been stated, the Negro problem socially, economically, and from the viewpoint of public health, has ceased to be a matter of interest to a limited portion of the country; it has, and is, yearly becoming more so, a national problem.

So far as public health measures are concerned, they must be inefficient if the health problems of this race are disregarded.

Those imbued with bitter racial antagonism are equally concerned with those who have a sincere desire to elevate these people. Two outstanding facts must be considered: (1) That in the city of Philadelphia for the year 1921 the death rate from tuberculosis among the Negro population was 299 per 100,000 as against 99.5 per 100,000 among the white population; (2) that syphilis, as indicated by the Wassermann reaction, is about 6 times as frequent among the Negroes as among the Whites. These figures can be duplicated and, in many instances, increased in other communities where the Negro population is large.

It is obvious, therefore, that a large field is open for effective antituberculosis work among Negros, for there is no reason to believe that the tuberculosis mortality rate need be so much higher among them than among the whites. It should be possible to bring the curves of the tuberculosis mortality rates for both groups much closer together than they are at present. This is borne out by the fact that twenty-five years ago the Negro mortality rate was much higher than at present and that during this period there has been a steady decline.

When one considers that this race furnishes large numbers of the servants in our homes, as cooks, nurses, maids, laundresses, etc., it would seem that some effort would be made to reduce the incidence of both infections.

Tuberculosis in the Negro is an interesting chapter in the etiology of this disease.

The history of the Negro in the United States dates back to August 1619 when a Dutch ship entered the James River and landed a cargo of slaves in the colony of Virginia. (Matas)—"Thus at Jamestown, twelve years from the settlement of the colony of Virginia and one year before the Pilgrim Fathers had touched the new world, began

that system in the British Continental Colonies, which under the fostering care of England, overspread the land. During the years from 1619 to the opening of the American Revolution, 1776, more than 3,000,000 African bondsmen were imported into the thirteen British Colonies."

In 1865, at the close of the Civil War, the slave population had increased to 4,000,000, and now, 1922, or three centuries after their first introduction to this country, the Negro population has increased to 10,463,131.

Among the early importations many diseases, notably yaws, elephantiasis, sleeping sickness, etc., were introduced but, owing to unsuitable climatic conditions these infections gradually died out and eventually became rarities.

The existence of tuberculosis among the original African and, indeed, among the slaves in the anti-bellum period was practically unknown. If one goes over the medical journals published during the first half of the 19th century, an occasional article will be encountered reporting "an undoubted case of consumption in a Negro." Furthermore, the rarity of the disease is almost universally attested to by those practicing in the South during that period. "To the question propounded to Dr. Cartwright in 1859: 'Is not phthisis very common among slaves of the Southern States and unknown among the native Africans at home?' he replied: 'That phthisis so far from being common among the slaves of the slave states, is very seldom met with'." (Matas.)

This is in accordance with accepted facts regarding the etiology of tuberculosis, namely, that the disease is unknown among the savage and primitive peoples and that the appearance of tuberculosis among them is coincident with their first contact with civilized whites.

The original African slaves, therefore, may be assumed to have been free from tuberculosis. That they remained so for the two hundred and forty-four years of slavery may be ascribed to the following facts: (1) They lived in agricultural communities and hardly at all in large centres of population; (2) reports to the contrary, they were almost universally well housed, well fed and safe guarded, in so far as possible from illness. The last consideration would be dictated by policy if not by sentiment as they represented property and extremely valuable property at that.

So far as one can learn, therefore, following the Emancipation Proclamation, the Negro population, which for the most part lived on the plantations drifted into the nearest city or town. Without resources and with little or no experience in fending for themselves it was inevitable that they should crowd into the poorest and most unsanitary quarters likewise they were not efficiently fed; and finally, and more important, they were brought into contact with the two diseases which have since exacted such a heavy toll of lives, namely tuberculosis and venereal infection.

In so far as tuberculosis was concerned the drama was that which has been enacted in so many other races. The implantation of the tubercle bacillus in virgin soil, no tolerance such as occurs in races exposed for centuries to the disease and, as a consequence, rapidity of the spread of the disease from individual to individual.

The ultimate result of the factors just cited has been to cause a tremendous morbidity and mortality rate due to tuberculosis.

As has been stated above it was the opinion of many that the inroads from tuberculosis alone would ultimately, and at no distant time, destroy the race. Time has shown this opinion to be fallacious. In spite of the high mortality rate from tuberculosis the Negroes continue to increase in numbers, and while there has been a decline in the death rate it is still abnormally high. Tuberculosis continues to be a serious problem with them and because of their association with the white no less a menace to the latter.

There can be scarcely any difference of opinion as to the far reaching effects of the modern crusade against tuberculosis. It is the first great effort directed towards the control of a universal disease; and, while in the beginning the sole object of the movement was to cause the disappearance of that disease, it has gradually broadened its scope until directly or indirectly most of the problems relating to public health are influenced.

In spite of the long duration and the intensiveness of the propaganda against tuberculosis, it is interesting to note that it has been, for the most part, effective only among the whites. The influence it exerted on the Negro population has been almost nil. The reasons for this are probably to be ascribed to the following facts: (1) No special meet-

ngs were held to directly interest them; (2) ittle of the literature on the subject appearng in the daily papers or the magazines was ead by them; (3) their aversion to going to lispensaries and hospitals; (4) and in my pinion the most important, the inability of he white nurses to influence them.

Whether these reasons are correct or not, he fact remains that in spite of the high inidence of the disease among them, institutions devoted to the care of tuberculous paients had relatively few Negroes and the few who visited the dispnsaries paid but one or wo visits and then ceased coming.

The Henry Phipps Institute of Philadelphia has always been located in the midst of one of the largest of the Negro settlements in Philadelphia. For the first ten years very few Negro patients came to the dispensary and those few rarely paid more than two or three subsequent visits. Most of the Negro patients we treated were those admitted to the Wards of the Hospital in a dying condition. A recent survey we made of the Negro situation in Philadelphia confirmed this in regard to other institutions having a large Negro population in their immediate neighborhood, namely, that after the initial call they rarely paid many subsequent visits.

This state of affairs began to interest us as far back as 1912. At that time the writer became associated with the Whittier Center, an organization having as its object the promotion of the health of the Negroes of Philadelphia. It was felt that something should be done towards attacking this problem and that something different was needed as the methods which had proved successful with the White population had failed.

It seemed to us that it was worth trying the experiment of carrying on an educational campaign among them through the medium of a colored nurse. This experiment began on February 1st, 1914. The following table shows clearly the effect of intensive work among them:

Mostly Ward Patients.		Colored Nurse Began Work.	
1904	47	1914	121
1905	28	1915	117
1906	76	1916	141
1907	57	1917	142
1908	49	1918	140
1909	67	1919	190
1910	37	1920	245
1911	48	1921	400
1912	45	1922 (8 months)	475
1913	57		

In July 1914, two additional nurses were furnished. At this time a special clinic was established at the Phipps Institute and was placed in charge of a capable colored physician, Dr. Henry Minton.

In 1920 the Philadelphia Health Council became interested in the venture and through its aid three additional colored nurses and two colored physicians were assigned to the Institute. At present we have a force of six nurses and three physicians working among the colored population. In addition the Jefferson Hospital for Diseases of the Chest has one colored physician and one nurse.

Recently, we have established a subdispensary in another district and are about to place a second one in still another area.

In addition to its specific problem of dealing with tuberculosis the Phipps Institute conducts a prenatal and postnatal clinic and a syphilis clinic.

Our experience with the Negro in these special clinics was similar to that in the tuberculosis dispensary, namely, few patients belonging to that race, so long as they were handled by white nurses.

The following tables show the growth of these special Negro clinics as soon as a colored worker was placed in charge:

Prenatal Clinic.	
1921—New Cases	28
1922—New Cases from February 1st to date	50

Prophylactic Clinic.	
1921—New Cases	83
1922—New Cases from February 1st to date	91

Syphilis Clinic.	
1921—New Cases	133
1922—New Cases from February 1st to date	77

A year ago we arranged to take each one of the graduating class of the Mercy Hospital (a Negro Institution) for a period of two months. While the time is short it gives these nurses some idea of the tuberculosis and public health problems.

It is interesting to note that the first nurse taking this course was sent to Wilmington, Delaware, to take charge of a Negro tuberculosis dispensary which had been a failure. As a result of her energy the attendance at this dispensary was tripled in two months and the dispensary days increased from one to three.

To further substantiate this there is the ex-

perience of the Jefferson Hospital for Diseases of the Chest. During the first six months of 1921 when the Hospital had only a part time colored nurse, who came to the Clinic once a week, thirty-nine (39) new patients visited the dispensary. During the second half of the year 1921, a full time colored nurse was placed in charge of the work and the number of new Negro patients who came to the clinic during this period was ninety-six (96) or nearly three times as many colored patients as were added to the roll the first half of the year.

Taking all these experiences into consideration, this deduction would seem warranted: That those Institutions that make use of Negro doctors and nurses for the care of patients of the same race are, from the standpoint of number of patients and regularity of their attendance, most successful in the treatment of Negro patients.

In a previous article on this subject the situation was summarized as follows:

As the matter stands at present, there is operating at the Phipps Institute a clinic held by and for Negroes (with expert white guidance and supervision) which is doing health work on the most modern lines and with a degree of competency which compares favorably with that of the average clinic for whites of the same kind. It is the only venture of the kind in this vicinity, and we know of no other like it anywhere. The general method of approach is that followed by most successful effort in connection with the Negro (as good a quality of endeavor by the Negroes themselves as can be secured with careful, sympathetic direction and supervision by whites).

The importance of the problem may be emphasized. Philadelphia has to-day upward of 140,000 Negro residents. They are only partially segregated. As servants, they go most intimately into many homes of the whites, and are a constant source of possible infection there.

When one considers that the mortality among this race ranges from 300 to 400 per 100,000 as against 100 to 125 per 100,000 among the whites, the problem is truly appalling.

1818 *South Rittenhouse Square.*

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AN EXPERIMENT IN THE EMPLOYMENT OF ARRESTED CASES OF PULMONARY TUBERCULOSIS

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Philadelphia

The fitting of those persons who have been handicapped by injury has received a tremendous impetus as the result of the World War, and vocational training or rehabilitation in behalf of those who have lost their sight or one or more limbs has become a governmental function.

The problem has been that of training them so that they could earn a living and compete on nearly equal terms with those not so handicapped. One of the essential facts to be borne in mind in regard to this group is, aside from their loss of sight or limbs, that they are otherwise organically sound. I desire to emphasize this because the same plan is now being advocated for arrested cases of pulmonary tuberculosis. It may also be remarked that there seems to be an impression in the minds of some that the idea of helping the arrested case of tuberculosis had been given no consideration until recently. It is partly because of this and partly because of the present interest in the subject that this report, long delayed, is now being made.

The problem of what should be done with the arrested case of tuberculosis is one that has bothered students of this subject for years. In many instances there is no difficulty. The patient may return to his former employment not only because he is physically fit but also because he will do better at his old trade or employment than at something new. Nevertheless, there always remains a considerable number about whom there is a problem. How much work can the patient do? What kind of work is best suited to his physical condition? Questions of this nature are constantly coming up.

It must be evident that there is a great difference between those physically handicapped but free from disease, and those suffering from a disease such as tuberculosis which can rarely be said to be completely cured and in which there is the ever possible danger of relapse.

The idea of rehabilitation or vocational training for arrested cases of tuberculosis is not new. One of the best illustrations of what has

been accomplished is that afforded by the training as nurses of women who have recovered from tuberculosis. When the tuberculosis crusade was definitely launched in this country nearly two decades ago it soon became apparent that one of the difficulties to be overcome was the nursing of the tuberculous sick. The emphasis placed on the danger of infection caused a more or less widespread fear of the disease. And this fear had not a little to do with nurses declining to enter institutions devoted to the cure of tuberculous patients. Not only did many of them have an exaggerated idea of the danger of contracting the disease but, in addition, they consciously or unconsciously showed this fear. Furthermore, they had little faith in the curability of the disease and were apt to take a pessimistic attitude toward their patients. It is only fair to say that many of the early experiences in this regard were gained through inefficient nurses who only too often took up the work from necessity rather than choice. The fact is undeniable, however, that the nursing work was unsatisfactory, inefficient and, quite as often as not, detrimental to the patient.

It was with the idea partly of overcoming this difficulty and partly of providing a suitable occupation for women who had sufficiently recovered to do the work required, that the Phipps Institute, then under the direction of Lawrence F. Flick, opened the first training school in 1904. It was hoped that these young women, having been cured themselves and having overcome the disease, would be no longer afraid of it. This school was successful from the beginning. It proved that the training could be undergone successfully and that the nurses brought to their work both enthusiasm and keen sympathy for the patients under their care.

In 1907 a similar school was started at the White Haven Sanatorium. That it is fulfilling the double purpose of not only providing efficient care for the patients in that institution but also furnishing nurses for other institutions is attested by the fact that the demand for graduates is always far in excess of the supply.

Successful schools of this kind are now in operation at the Adirondack Cottage Sanatorium, Trudeau, N. Y., and a number of other institutions.

This somewhat lengthy introduction has seemed necessary in order to explain the reasons which led the Phipps Institute to conduct the following experiment, which represents the experience of the Phipps Institute in a further effort to develop suitable employment for arrested

cases of tuberculosis. The experiment was started April 1, 1914, and closed July 1, 1916. The possibility of utilizing arrested cases of tuberculosis in some form of industry that would make them altogether or in part self-supporting suggested itself as far back as 1911. During the latter year a night tuberculosis class was conducted at the Institute in the interests of patients who had recovered from their acute symptoms under dispensary or tuberculosis class treatment and of returned sanatorium patients. Inasmuch as some 80 per cent of the patients seeking relief at the Institute are foreign born, for the most part Russian Jews, a very large number of people engaged in the various branches of the ready-made clothing industry are encountered. It was our experience in watching these patients over a period of years that many of them were able to return to this vocation, resume their wage earning capacity and at the same time maintain their health, provided they were supervised and were at all amenable to discipline. At the same time it was noted that a certain proportion seemed unable to withstand the strain of keeping pace with their fellow workers who were normal. It seemed logical therefore to try to provide some means of giving sufficient employment to this handicapped class to take them, if possible, out of the group *entirely* dependent on the aid of the charity organizations.

The situation then and now, for that matter, was that industry as at present organized has no place for the man and woman capable of working, with safety to their health for only four, six or eight hours a day. They must either accept the risk of breaking down on full time or seek relief from one of the charity organizations. In some instances the acceptance of aid from the latter is taken as a matter of course, but with not a few the feeling that they have to depend on charity is deeply humiliating. Whether the charity is accepted willingly or unwillingly it usually happens in the end that the moral fibre of the individual is destroyed; and he not only accepts the aid but is also likely to take the point of view that such assistance is his right. To prevent the development of this attitude, in so far as is possible, is important not only from the standpoint of the individual but also to relieve the terrific strain on society in caring for these people. While there may be a certain amount of sentiment in aiding in the uplift of the individual, the problem, in so far as society is concerned, is an intensely practical one. As the income of charity organizations is raised almost entirely by subscriptions, every additional case to be cared for increases the burden by just that much.

If, therefore, the means is provided of permitting the handicapped to earn at least a part of his living two purposes are served. In the first place the fact that he is at work and doing the best he can under the circumstances strengthens his self respect. In the second place, every dollar so earned decreases by that much the burden imposed on the charity organizations.

The idea of starting an experimental workshop had its inception, therefore, in the experience which has just been stated.

The general idea of providing the means of livelihood for those situated so that they cannot compete with the normal worker is not a new one. Several sanatoria for the treatment of tuberculosis, for instance, have established as a part of their equipment some such scheme. In some instances it has taken the form of a workshop where certain light forms of work, such as bookbinding, etc., may be undertaken during the period the patient is under treatment. Only in a relatively few instances, however, has the work been undertaken with the idea of permanently employing such people and attempting at the same time to make the venture self-supporting.

Profiting by some of these tentative trials it seemed apparent that any such scheme must first deal with some commodity for which there is a steady demand. The commodity must be a staple one and not one for which there is a limited demand. Furthermore it must be one the buying of which is not dictated by sentiment. Several ventures which were highly successful for a year or so finally failed for this very reason. Their output was taken by a small group of interested persons but no real market was created. In the end they failed because those who originally bought had no use for any more of the product and new buyers could not be obtained.

Partly for the reasons just stated and partly because so many of the people with whom we had to deal were or had been employed in some branch of the ready-made clothing industry, we determined to try some feature of this trade. Our first selection of the article to be manufactured was not a wise one, although practical people whom we consulted did not in the beginning warn us of what we soon learned ourselves and what still others told us later. In the beginning we essayed to manufacture a cheap form of shirtwaist. It was not difficult to make, the material was inexpensive and did not involve the locking up of a large amount of capital and, in addition, it seemed to be an article for which there was a large and constant demand.

What we did not foresee, however, was the fact that of all commodities there is hardly another one which is so subject to the vagaries of changing fashions as the shirtwaist. What is a readily salable waist to-day is out of date to-morrow, and poorer women are almost as insistent in their demands for the latest style as their wealthier and more fashionable sisters.

As this venture proved unsatisfactory financially, we cast about for some article for which there was a more steady market and which, as it is spoken of in the trade, is staple.

The manufacture of hospital supplies was suggested but inasmuch as the demand for this class of goods is relatively limited and was already amply made in sufficient quantity, no attempt was made to carry this plan out.[1]

The making of aprons was tried for a time, but their cheapness makes it necessary to produce them in large quantities in order to make even a small return on the venture. Furthermore, a large output was not possible with people incapable of working long hours and also unable to work at top speed. In this connection it may be said that much of the evil incident to the manufacture of ready-made clothing in its various branches, lies in the so called "speeding-up" process. The more the manufacturer can turn out daily with the same expenditure of power, the larger the profits. The more the worker can produce, the higher the weekly wage and, in order to accomplish this, the work must be carried on at top speed day in and day out. It is this factor more than anything else that renders the individual with a lowered resistance incapable of maintaining his health. After consulting with a number of manufacturers and salespeople, we finally decided upon the manufacture of women's black underskirts. This particular article is always staple and practically never changes. With the selection of this article, our problem was solved in so far as obtaining a salable article was concerned.

FEAR OF INFECTION

From the very beginning one of the most serious obstacles we encountered was the prejudice against handling any article of goods manufactured by people who had or had had tuberculosis. Even when it was carefully explained that they were either closed cases or cases in

[1] The workshop for arrested cases of tuberculosis conducted by the United Hebrew Charities of New York City has within the past two years made this specialty a success.

which all cough and expectoration had ceased, the objection held. Furthermore, when we stated that our experience in making a survey of the ready-made clothing industry showed very clearly that many of the small, so called sweatshops, doing subcontract work for larger firms, were often extremely unsanitary and that open cases of tuberculosis were not infrequently encountered among the workers, prospective customers remained unconvinced. As a matter of fact, one of the worst of these subcontract shops we encountered was doing work for a large firm which made a point with the public of advertising clothing produced under ideal sanitary conditions. The argument used by the heads of departments in several of the department stores which we visited was that if they should place on sale goods so made and it became known, this fact would be used to their disadvantage. Failing to obtain cooperation in this direction we were forced to address ourselves to the small jobbers who supplied goods to the small retail stores scattered throughout the city. The financial status of these jobbers we later found was not always of the best. In several instances we suffered a loss because of inability to collect our bills; in others, the final settlement was a compromise; and in nearly every instance considerable difficulty was experienced in getting our money. Eventually, when the manufacture of skirts was undertaken satisfactory arrangements were made with a large and responsible house. In this instance the goods were taken, as they were from other small jobbers, without anything being said as to where they came from. The shop simply played the part of a small subcontracting establishment, an arrangement which prevails throughout the ready-made clothing industry.

FOREMAN

Because of the small size of our shop it was necessary to obtain a foreman who could at the same time cut out the goods. The man whom we first employed had had a large experience, and had been for some years a cutter and acting foreman in a moderate-sized shirt waist factory. He had two serious defects, however. Unfortunately he lacked ability to control the workers and was constantly appealing to us for aid to straighten out disputes. Furthermore, he lacked intelligence, especially from the point of view of grasping the idea of the experiment; and again he was utterly lacking in business judgment, both in the buying of material and in the sale of it after it was manufactured. Many of our

original financial disasters can be attributed to this fault. Later this defect was remedied. A serious business error was that the wage paid the foreman was entirely out of proportion to the size of the shop.

EMPLOYEES

As we determined in the beginning to deal with some article of women's apparel the workers were restricted to women. These were selected from our dispensary or discharged ward cases. In several instances we utilized women patients from the wards who had become at least symptomatically cured. They were usually employed for a part of the day and the work was prescribed as a form of exercise. Among the dispensary patients we attempted to limit our choice as follows: They must be free from expectoration and they must be dependent on charity. It became clearly evident from the beginning that many of these women were averse to the idea of working. Even when it was explained to them that the charity organization would continue to aid them and that by earning as much more they could better provide for themselves and their children, if they had any, they still refused. As the majority of our women patients were Jewish, it was suggested to the United Hebrew Charities that they coöperate with us and that in the event of a woman's refusing to work they withhold their assistance. We assured them that we had no idea of either recommending that they withdraw aid or that we desired to employ anyone who would be seriously injured thereby. This was agreed to, but unfortunately, after a few abortive attempts in the beginning, the plan failed.

This is one of the most important points in such a plan. There are a surprising number of people who do not want to work if they can avoid it. They prefer a pittance to an adequate weekly sum if they can obtain the pittance for nothing. It becomes necessary, therefore, to apply some pressure in such cases. This can best be done by the dispensing power also making the decision of whether they are fit to work or not. If the former is the case it is an easy matter to issue the dictum, "Work or no support."

The later success of the New York Hebrew Charities in an experiment similar to this can, we believe, be attributed largely to the fact that they both dispensed the charity and controlled the workers in this way.

From the very beginning it seemed reasonably clear to us that to compete with others manufacturing a similar line of goods it could hardly

be expected that we would make money. Such ventures must probably be expected to show some deficit. Success will be indicated, therefore, by a low annual deficit. This is obvious because of the fact that in no case is a force such as we are considering capable of working at top speed.

In conversation with an experienced manufacturer he pointed out that the successful factory manager depends for his profits on the high-class rapid operator who is paid from $14 to $18 per week (wage rate, 1914–1915). This type of worker produces better work and two or three times the quantity turned out by the less skilled operator. At the same time the overhead charges for the one skilled operator amount to only one-half or one-third of the charges necessary for the amount of work. The minimum number for a small shop should be in the neighborhood of 30, whereas we started with 10. As has already been pointed out, it is the operators capable of producing a large quantity daily who offset the work of those less skilled. Attempting to conduct a shop with a force made up of "cripples" who are, more often than not, of the unskilled type, is a handicap which is hard to overcome. This difficulty may be surmounted, in part, by employing healthy, skilled operators in the proportion of, say, one to five. Such an arrangement would improve the character of the work by the supervision these skilled workers could give the less experienced and at the same time insure a larger output. We finally came to this plan after nearly a year's experimenting with the handicapped only.

WAGE EARNING CAPACITY

It was realized from the outset that these women would be unable to earn sufficient to entirely cover their support. As has already been stated one of our objects was to enable these handicapped persons to contribute to their support in part only, certainly until they could be gradually brought up to a point where their physical condition would warrant greater efforts.

In selecting workers we restricted ourselves to those who were patients at the Phipps Institute dispensary. This undoubtedly prevented us from availing ourselves of many skilled workers who had been discharged from sanatoria with their disease arrested, and who returned directly to their former place of employment without going to a dispensary for observation. In but two or three instances did we have women who could be termed "skilled" and these, unfortunately, were

not strong and were therefore incapable of producing more than an average output. It is interesting to note that one of these women, feeling that she was not making sufficient with us, returned to her regular place of employment in order to earn more money. She quickly broke down, however, and for a second time returned to our shop.

All of the women whom we employed, with one or two exceptions, were physically below par, and as such, could not be expected to equal the output of even the average operator. Our greatest handicap, however, was the fact that these women, even if physically sound, would still have been poor workers. Partly from lack of any education with its resulting ignorance, and partly because they were mentally stupid, it was almost impossible to instil into them any ambition to aid themselves. They are representative of the type that plagues all employers. With good health they would be inefficient; somewhat broken in health and already used to obtaining aid for which no equivalent was given, they could not be aroused to a sense of independence.

In all, we employed at one time or another twenty-five to thirty women. Some worked four, some six, and some eight hours. They earned from one-third to over one-half the standard wage of that time. In no instance was their health impaired.

MEDICAL MANAGEMENT

It goes without saying that the medical side of such a plan is important. The doctor must pass on the person to be employed (1) as to whether acceptable; (2) if acceptable how much work he or she can do; and (3) with the physician must rest the decision as to whether the work can be increased or whether it must be stopped altogether. With the health of the employees the function of the medical advisor ceases.

BUSINESS MANAGEMENT

As already pointed out the minimum for a shop should be thirty. Any number under this increases the overhead charges too much.

It is essential that the business management be entirely in the hands of a man with experience in the manufacture and salesmanship of goods. One of our difficulties in the beginning was in having a foreman who had no judgment in regard to buying material or in selling the finished product. Our second selection was very satisfactory.

FINANCIAL STATEMENT

This experiment is divided into two periods. As will be seen from the table the first period was anything but a success financially. This is to be ascribed to three factors: (1) poor business management much of which must be charged to the writer who attempted to engage in a venture about which he knew nothing and also in relying too much on an inefficient foreman; (2) experimenting in the selection of a salable article; and (3) in employing a working force entirely made up of handicapped and also, in some instances, inexperienced workers. The second period shows clearly the great reduction in the deficit affected through eliminating the faults of the first period.

First period

Expenditures: March 1, 1914, to final payment in September, 1915, as follows:		
Equipment, 1/2 charged to	$401.18	
Merchandise	2,114.53	
Wages, operators	1,742.64	
Wages, foreman	1,346.50	
Rent	390.00	
Expenses (Light and power, expressage, cleaning, etc.)	398.98	
		$6,393.63
Receipts: March 1, 1914, to final settlement of accounts in February, 1916		3,368.08
Deficit		$3,025.55

Second period

Expenditures: November 1, 1915, to final payment in August, 1916, as follows:		
New machinery	$1,231.18	
Machinery sundries, repairs, etc.,	117.78	
Merchandise	8,468.42	
Wages, operators	1,322.21	
Wages, foreman	830.00	
Rent	350.00	
Expenses (Light, and power, expressage, cleaning, etc.)	536.20	
		$12,855.79
Capital: November 1, 1915,	$1,321.15	
Receipts: November 1, 1915 to final settlement of accounts in March, 1917	11,289.16	12,610.31
Deficit:		$245.48

Note: On July 1, 1916, there was a deficit of $3,067.99, but by sale of manufactured goods and raw materials on hand, also equipment, this amount was reduced to $245.48, as above.

SUMMARY

In an effort to acquire further experience with the practical problem of employing arrested cases of tuberculosis in industry we organized and operated for about two years a small shop for the manufacture of ready-made wearing apparel. The operation was conducted in two periods. The first period was a failure in the financial sense. In the second period enough was done to show that better financial results might be secured under favorable conditions.

From the social point of view our experience developed important suggestions as to the requirements underlying and bearing upon any similar venture.

From the medical point of view the experiment was an unqualified success.

In support of the above general statements, we would call attention to the following specific points:

Medical:

1. The arrested case of tuberculosis (and certain others physically handicapped) may be employed in industry with no detriment to their health and often to the advantage of it.

2. To accomplish this the arrangements for their employment must be sympathetic and such that they can work part time.

3. The actual time they are to be employed must be under the control of a physician and he must put health questions before business questions but must have regard for the latter.

Social:

1. Such employment benefits society by its tendency to avoid pauperization of a group with the strongest tendency to compute economic and moral dependence.

2. Any such scheme is impossible of successful operation without the careful coördination of the charity organizations of a community, as pressure must be applied from time to time in those so reduced morally that they prefer accepting charity to working.

Business:

1. Considering the size of this problem and the intellectual qualifications of most of those in need of aid, no such venture can be a success which undertakes to manufacture objects of art or other specialties the demand for which is dictated by fashion.

2. Staple articles, on the other hand, while they must be the basis for such an operation, are manufactured under high pressure and marketed under highly competitive conditions. If these conditions are to be met the workers must be employed at high speed for whatever time they are at work, and a fair proportion of skilled healthy workers must be employed to set standards and take up the slack.

3. The actual business management must be in the hands of a very competent person from the business point of view (because of the competition) and he should at the same time be of unusual intelligence in order to adapt himself to the health requirements of the workers and secure the primary object of the operation.

4. Such a venture would need for a fair chance of success considerable working capital and the sympathetic coöperation of the business men of the community, at least those concerned in the same manufacturing field.

CONCLUSIONS

1. This and similar ventures have shown that arrested cases of tuberculosis can be employed to advantage without detriment to their health if properly supervised medically.

2. It is necessary to delegate to a business man the entire management of the commercial side of the problem.

3. From the economic side this experiment can be said to have been a success. The deficit was small. This could have been much larger and still have made the experiment worth while.

END RESULTS OF SANATORIUM TREATMENT FOR TUBERCULOSIS*

H. R. M. LANDIS M. D., PHILADELPHIA

The value of sanatorium treatment of tuberculosis and, more particularly, the ultimate results of this method of treatment have been the subjects of adverse criticism. The charge is made from time to time that the sanatorium has failed to accomplish what was originally, and what is still claimed for it. It may not be amiss, therefore, to examine into the facts of the case.

Although it is true that here and there there were men who appreciated the basic brinciples upon which the treatment of tuberculosis depended, it was not until Briemer established his sanatorium at Görbersdorf in 1858 that the treatment became crystallized into the form that now exists. There have been certain changes in the details of the treatment but the underlying principles have undergone but little change . The extension of the sanatorium was a gradual process. In this country it was not until 1884 that the first one was put into operation and for some years it was the only institution of the kind in the United States. With the launching of the modern crusade about fifteen years ago the number of sanatoria, both public and private, increased rapidly.

Much of the criticism of the sanatoria today is based on the failure of these institutions to fulfill what was unwarrantedly claimed for them in the beginning. These institutions were to care only for the early and supposedly curable cases of tuberculosis. By so doing the number of individuals who gradually progressed into the advanced and open stages of the disease would be rapidly diminished and in this way the infection of others would be correspondingly reduced. From the beginning, however, this hope failed to materialize. There was hardly an institution that did not receive a fairly large quota of moderately advanced and even far advanced cases. In some instances this was due to a mis-

* Read before the Section on Medicine of the Medical Society of the State of Pennsylvania, Pittsburgh Session, October 6, 1920.

conception of the physician referring the cases as to what a favorable case was; in others the desire to keep the beds of the sanatorium filled led to a more liberal interpretation of the type of case to be admitted. The result has been that, with few exceptions, tuberculosis sanatoria throughout the country contain a relatively small number of true incipient cases. One of the effects of this is that the number of patients who relapse after leaving the sanatorium increases in direct proportion to the number of cases beyond the incipient stage. This, of course, leads many (both physicians and laymen) to conclude that sanatorium treatment is not very effective.

Furthermore while the mortality rate from pulmonary tuberculosis is gradually falling, it has failed to decline at the rate that many once confidently predicted; and for this the sanatorium comes in for its share of the blame. In my judgement this is a wrong conception of the case. In our zeal to promote the prevention of tuberculosis we are apt to lose sight of the fact that we, as physicians, are under the serious obligation of trying to bring about a cure or to prolong life or to alleviate the sufferings of those who have developed the disease. Our duty toward these individuals is quite as urgent as that of trying to prevent the occurrence of the disease in others. For this reason, if for no other, the sanatorium is an essential cog in the machinery for dealing with the tuberculosis problem. It does play a part in prevention and it is one of the effective methods, and in some instances the only available means we have, of restoring the tuberculosis patient to health.

Almost from the onset I have been a strong advocate of home treatment but I realize fully that there are many, many individuals who are unable to satisfactorily carry this out. The single man or woman living in a boarding house, for example, cannot be treated in his or her lodgings; or the home conditions may be such that it is impossible to obtain even the simple requirements essential for the treatment; or well-to-do patients cannot always be divorced from social distractions or business worries unless they are removed from their home surroundings. Finally there are many who will carry out the details of treatment in the home if they have had a preliminary course of treatment in a sanatorium. I am speaking now of sanatoria in which there is an intelligent effort toward individualization in treatment and in which the essential features are adhered to. There are, unfortunately, some sanatoria in this

country in which there is little or no effort made to treat the patients individually. Some of them cannot be considered as other than isolation institutions in which the patient does pretty much as he pleases and, if recovery does take place, it can be ascribed to accident and not to any special help from the institution. If I were to single out the one great advantage which the sanatorium offers I should unhesitatingly say "rest." Under no other circumstances can one be as sure that the preliminary rest treatment and the subsequent exercise tests will be as well looked after as in a well-conducted sanatorium.

I think that the greatest disappointment from sanatorium treatment, aside from the part it plays in prevention, has been the frequency of relapses among those who have undergone such a course of treatment. For the most part criticisms of this sort are not warranted by the facts. The question of relapse must be considered from several viewpoints. In the first place one of the characteristics of pulmonary tuberculosis is the tendency to relapse. This has led to the abolition of the term "cure" and the substitution of "arrest of the disease," the latter indicating that it may be temporary or permanent but that there is no assurance that the disease will not recur, especially if the patient fails throughout the rest of his life to adhere to certain simple rules of living. It is this tendency to relapse and a failure to appreciate the factors that bring about a recurrence of the symptoms that have led to confusion as to sanatorium results.

In the first place it must be clearly understood that the sanatorium itself has relatively little to do with the occurence of relapses unless it restricts its admissions to the type of case in which the preliminary damage to the lungs is of the slightest. Such an institution will naturally be able to point to a far larger percentage of arrested cases than the one which admits a number of moderately advanced cases. Again the institution that receives a large proportion of well-to-do patients, whether of the incipient or moderately advanced type, will have fewer relapses than that dealing with those who must return to work. The well-to-do can always regulate their lives and restrict their activities in accordance with their physical disability, while those dependent on their labor for support must inevitably take their chance of breaking down. The condition of each group on discharge from the sanatorium may be identical;

it is their manner of living after leaving the sanatorium that determines, largely, whether they remain well or relapse.

There are a number of causes which bring about a relapse. Some of these are beyond the control of the patient while others may be directly charged to his fault. One of the most frequent causes of a relapse is insufficient time given to the treatment. In some instances this is the patients fault; in others it is beyond his control. It not infrequently happens that, as the result of rest and regular living habits, the patient is quickly relieved of his symptoms and rapidly gains weight. His fears are, therefore, allayed; he becomes unduly optimistic and it is difficult to convince him that the pulmonary lesion, in spite of the disappearance of the symptoms, has not had sufficient time to become fibrosed. Such a case may relapse very quickly unless the initial lesion is of very slight extent. Again the symptoms clear up very slowly and the patient lacks the perseverance to prolong the treatment.

Finally, there is a large group which cannot stand the financial drain or if in a free institution, feel, that at all hazards, they must take up the burden of providing for their families.

Of those causes for which the patient himself is responsible, it is not necessary to go into details. We are all familiar with the invidual who within twenty-four hours of his leaving a sanatorium has made the tentative beginnings of returning to his former methods of living. Dissipation is not by any means the chief of these. More often it consists in a failure to secure sufficient rest; to become careless as to his dietary requirements; or to be tempted by higher wages to attempt work which is beyond his strength.

The educational advantage of the sanatorium has been said to be over-rated and to substantiate this, examples are cited of what many patients do or fail to do on leaving such an institution. All I can say in answer to this is that, if any intelligent individual by reason of his surroundings, the routine imposed upon him by a well conducted sanatorium and the verbal teaching given, fails to have learned what is essential for him to remain well, I know of no other method that can be expected to accomplish this.

In addition to the hazards which the patient can avoid if he so desires, many people have their chances endangered through causes which they cannot altogether control. Thus some acute intercurrent illness or, as in several cases I have had, a violent nervous shock may bring about a recurrence of the symptoms and a

spread of the pulmonary lesion. Relapses occurring under these conditions are, of course, unavoidable and constitute one of the risks to which every tuberculous individual is liable.

Aside from the causes controllable by the patient the most potent source of a relapse is the effort of the handicapped wage-earner to provide for himself and his family. This difficulty could be minimized considerably if more time were given to obtaining a better pathological arrest of the disease. By this I mean the time needed to secure sufficient fibrosis to wall off the pulmonary lesions.

As to the character of the work a tuberculous individual shall do there is still a good deal of misapprehension. Outdoor jobs are still advocated. Those of us who have had much to do with the post-sanatorium treatment of tuberculosis have long since realized that outdoor employment is a snare and a delusion. Work of this kind, when at all suitable, is limited; it almost invariably entails considerable physical exertion, and this, as a rule, is to be avoided for some time and in many instances is never advisable. The best rule to follow is that the patient, if he be a clerk, a taylor, etc., shall return to that work.

Within the past six months I have been consulted by two service men. One was a graduate pharmacist, the other a licensed marine engineer. Both were advised by the vocational Training Department to take a course in salesmanship. It was represented to them that employment of this nature would enable them to spend the greater amount of their time out of doors. That neither of them had any desire to change their employment, in which both had excellent opportunities, or that keeping out-of-doors meant being on their feet constantly did not seem to enter into the question at all. I advised both of them to stick to what they could do best and while I cannot say whether or not they will relapse, I am quite certain that their chances of so doing have not been increased.

Given the type of case which offers a chance of being improved, I think it can be said safely that the well-conducted sanatorium does all that has been claimed for it. Can the ultimate results be improved? This can be accomplished only by a well-organized follow-up system. There is no doubt that patients, whether from a private or a free institution, are prone to neglect consulting anyone once they have been discharged. Those of the working classes, especially, should be urged to report to a dispensary or their physician at once on their retutn home, in order that

their present condition may be noted. They should be visited by a nurse and they should report at the dispensary at certain stated intervals. For the great majority constant supervision and constant reiteration of the rules of right living are essential. I am quite aware that follow-up work is done but, in too many instances, it is perfunctory and consists of little more than a report of conditions with little or nothing done to remove unfavorable conditions or to maintain the discipline needed to keep the patient well. Furthermore there is often a considerable amount of social service work necessary. All this means that there must be an efficient corps of nurses maintained. For the most part this is not possible for the sanatorium but must be carried out by the particular community to which the patient belongs.

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Non-tuberculous Complications of Tuberculosis

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In considering the non-tuberculous complications of tuberculosis I shall make no attempt to cover the entire list, but confine myself to those which in my experience have been encountered most often. There are many traditions handed down to us in regard to the rarity or the frequency with which certain conditions occur in tuberculosis. For example, it has been long believed and is still believed that a gouty individual rarely becomes tuberculous; on the other hand it is known that diabetics are quite apt to become so. The truth of the matter is that, with few exceptions, there is scarcely a disease, whether acute or chronic, that may not develop in an individual who has either active or latent tuberculosis. Some diseases occur so infrequently as to be viewed in the light of rarities; others are combined with tuberculosis so frequently that in any considerable number of cases of the latter disease they will be encountered quite often.

It is essential that those who handle tuberculous patients should have a knowledge of these more common complications. In the first place, methods of treatment often must be varied to meet the particular indication. In the second place, a latent and unsuspected infection may retard improvement and may be the actual cause of a persistent fever, for example, which is wrongly attributed to the tuberculous lesion. Those of us who are constantly seeing tuberculosis must always be alert to the possibility that there may be other contributing factors, and this is especially true in those cases in which the symptoms remain stationary or undergo exacerbations from time to time.

Diabetes.—It has long been recognized that diabetes and tuberculosis occur relatively frequently in the same individual. It is a difficult combination to deal with. Prior to the introduction of the modern method of handling diabetes the usual procedure was to ignore the diabetes and, with perhaps a few minor restrictions as to diet, follow the course usually prescribed for tuberculous individuals. The results were almost universally bad. In dealing with this complication the first requisite is to control the diabetes. Unless this is done little or no progress can be expected.

The management of tuberculosis under these circumstances presents an interesting problem. The treatment of tuberculosis rests on three basic principles: rest, a generous diet, and an abundance of fresh air.

In diabetes, on the other hand, the patient is either starved for a brief period or placed on a restricted diet. Under the best of conditions the total amount of food one can give these patients is far below that usually thought necessary for a tuberculous individual. Furthermore, a moderate amount of exercise is desirable for the uncomplicated diabetic.

It can be readily seen that in dealing with this combination of diseases we must put aside one of the three main objectives aimed at in the uncomplicated cases of tuberculosis, namely, a gain in weight. Instead of gaining these patients will inevitably lose weight, sometimes alarmingly so. Nor can this loss as a rule be entirely restored owing to the relatively low intake necessary to keep them sugar-free. As a compensation for the loss of weight the patient improves in other respects, especially as regards toxic symptoms (fever, tachycardia, sweating, etc.).

While my experience up to the present time is limited, directly or indirectly, to

about thirty cases, I am still convinced that the control of the tuberculosis in such cases is absolutely dependent on getting the patient sugar-free and keeping him so. It is, of course, to be borne in mind that either one of the diseases may be so severe as to preclude recovery even if existing alone. But even in the inevitably fatal case they can be made more comfortable if the diabetes is first controlled.

Pregnancy.—There is no phase of the tuberculosis problem that is more important to the general practitioner than that of pregnancy, as the incidence of the pathological and the physiological condition is a frequent one. In 1913 Bacon estimated that 32,000 tuberculous women became pregnant annually in the United States, and added that between 44,000 and 48,000 women of the child-bearing age die of tuberculosis every year. There is no doubt, in my opinion, that pregnancy does exert a distinct influence on the occurrence of tuberculosis in women. Several years ago I studied a number of women at the White Haven Sanatorium, and found that over twenty per cent of those who had borne children dated the onset of their disease from a pregnancy.

A latent tuberculosis may be activated or an arrested case may relapse as the result of pregnancy under the following circumstances: In one group the tuberculosis may manifest itself during the pregnancy, often within the first few months. In the other group the woman remains well during her entire term, but shortly after confinement develops pulmonary symptoms, often extremely acute in character.

Why the symptoms develop during pregnancy is not clear. In some instances it would seem to be associated with the exhaustion and lack of nourishment due to severe vomiting, but in others there is no such factor. In those who manifest evidences of the disease following confinement, the violent exertion that characterizes many labors is commonly accepted as the probable cause of arousing to activity a latent lesion.

If one reviews the literature on this subject, the outlook is not promising. This is to be ascribed to the fact that the majority of pregnant women are delivered either by the general practitioner or by the midwife, and only a relatively small proportion are seen by the specialist. It naturally follows that the specialist is called in consultation in the worst cases, and that the worst cases are likely to be sent to hospitals for delivery, where again they fall into the hands of the obstetrician. Thus the obstetrician is especially prone to see those patients who are doing badly, and this is doubtless a factor in the high mortality and morbidity as usually reported in this condition.

The results obtained in the Prenatal Clinic at the Phipps Institute present an entirely different picture from that usually painted. In a report made by C. C. Norris and myself five years ago, we dealt with 85 cases. These cases consisted of about the ordinary run of pulmonary tuberculosis and were not of the class usually seen by the obstetrician.

Of the 85 cases, 69 or 81.1 per cent showed no change as the result of their pregnancy; two patients became worse and six died. In three cases the pregnancy was interrupted as the result of the pulmonary condition.

In dealing with this combination one has the choice of three different opinions: (1) That the uterus be emptied in all cases regardless of whether the patient presents symptoms of active tuberculosis or not. (2) That under no circumstances shall the pregnancy be interfered with. (3) That one shall pursue a waiting course. If there are no symptoms allow the pregnancy to continue. If, however, the woman develops symptoms which persist and become worse a therapeutic abortion should be done, providing the pregnancy has not advanced beyond four months. If not seen until after the fourth month, interference is not advisable, as emptying the uterus in the later months of the pregnancy has little favorable effect on the pulmonary lesion.

The last named course is the one we

have adopted at the Phipps Institute, and, as already mentioned, active interference has been deemed necessary in but three of 85 cases. It is fair to state, however, that this number would probably have been greater had some of the women been seen prior to the fifth month of the pregnancy.

Nephritis.—Some evidence of chronic inflammatory changes in the kidneys is present in the great majority of cases of pulmonary tuberculosis coming to autopsy. During the terminal minutes of the disease traces of albumin and the presence of a few hyaline or finely granular casts are commonly present in the urine, but it is rare, in my experience, to meet with severe grades of nephritis in tuberculous individuals. I cannot recall more than two cases in which the kidney functions were seriously disturbed. In both these cases there were large amounts of albumin, numerous tube casts, a scanty output of urine, and marked edema. In addition functional tests showed an extreme grade of retention. The dietary restrictions in these cases make them even more difficult to handle than diabetics.

Heart Disease.—Nearly three-quarters of a century ago Rokitansky enunciated the doctrine that venosity of the blood was antagonistic to the development of pulmonary tuberculosis. Among the conditions producing venosity he included all forms of heart disease, both acquired and congenital. Since his time there have been many observers who considered that left-sided heart lesions, especially mitral stenosis, did exert an inhibitory action on the growth of the tubercle bacillus. A number of studies have been made to prove or disprove this fact. Norris (G. W.) after a full review of the literature and study of a large number of autopsy protocols concluded that heart disease exerts little if any influence on the pulmonary lesion either curative or inhibitory. C. Y. White, in a study of autopsies on tuberculous individuals dying at the Phipps Institute, found that the valve leaflets were functionally disabled in six per cent of cases. In his opinion passive congestion of the lungs does not exert any effect on the development of tuberculosis.

In discussing the relationship between cardiac disease and pulmonary tuberculosis there are three types of cases to be considered: (1) Pure cardiac cases; (2) those in which there is an obvious cardiac lesion and possibly a latent pulmonary infection; and (3) those in which cardiac disease and tuberculosis are undeniably present.

It is well known that mitral stenosis especially is apt to be mistaken for tuberculosis because of the cough, blood-spitting, often loss of weight, and the presence of râles. As a rule it is not difficult to determine that the cardiac lesion is the real cause of the trouble. In a certain number of instances physical signs may point to the possibility of an associated tuberculous lesion. Sputum examinations and consultation with a roentgenologist will determine whether one has to deal with a complicated or uncomplicated case.

Within the past year I have seen two cases of mitral stenosis with fibrillating auricles and with tubercle bacilli in the sputum. My own experience is that individuals with enlarged hearts, definite valvular lesions and pulmonary tuberculosis are encountered relatively frequently, and that there is little to warrant the view that cardiac disease is antagonistic to tuberculosis.

When the two conditions occur together the treatment of the tuberculosis is that of the uncomplicated case, although occasionally one is encountered that stands even moderate altitudes very badly. If the compensation shows signs of breaking one should proceed as though the case were uncomplicated.

Syphilis.—It is inevitable in view of the frequent incidence of both syphilis and tuberculosis that these two diseases will be encountered often in the same individual. It has long been recognized that when both conditions are active in the same person the combination is a vicious one. Distressing examples of this are sometimes seen in

young prostitutes. When tuberculosis develops in an individual with an old and long-standing luetic infection the tuberculosis does not differ essentially from that occurring in an individual free from syphilis. This fact should be kept in mind, however: many, if not most, of these individuals should receive antisyphilitic treatment. In not a few of them the syphilis, although latent and presenting none of the common stigmata, may at the same time exercise a retarding effect on improvement just as a chronic focal infection.

The frequency with which tuberculosis and latent syphilis exists in patients coming to the Phipps Institute has made it a necessity for us to establish a special treatment clinic for this group. This necessity has arisen largely because of a very large Negro clinic, as it is well known a dual infection in members of this race is very common.

Our procedure is as follows: If the patient is tuberculous the initial dose of arsphenamine is 0.3 of a gramme. If this produces no untoward effects the subsequent doses are 0.6 of a gramme. Six injections are given, and then the patient is placed on some form of mercurial medication for six weeks. If the Wassermann reaction remains positive both courses are repeated. Many of these chronic luetic cases are extremely difficult to get Wassermann-free. If after repeating the treatment the reaction remains positive they are advised to repeat the single course of treatments once a year.

Iodide of potassium is never used in luetic individuals who in addition are tuberculous. In my judgment the use of this drug in the presence of a tuberculous lesion is dangerous. I have seen latent arrested cases of tuberculosis aroused into activity by the administration of small doses of iodide of potassium for diagnostic purposes.

Pneumonia.—Pneumonia in its relationship to pulmonary tuberculosis presents two problems: (1) That of distinguishing between true lobar and tuberculous pneumonia, and (2) that of determining whether in a tuberculous individual an acute febrile attack associated with signs of consolidation in previously healthy lung tissue is the result of a lobar pneumonia or a rapid extension of the tuberculous process.

It is not sufficiently appreciated that pulmonary tuberculosis often first manifests itself as an acute infection. There may be a chill or chilly sensations, a rapid rise in the temperature, and a corresponding quickening of both the pulse and respiration rates. In addition there may be blood-streaked sputum. Associated with these symptoms are signs of partial or complete consolidation in one lung, and (this should be emphasized) it is usually an upper lobe involvement. Such a case may terminate in several ways: (1) It may progress rapidly and terminate in a few months or even weeks as an acute tuberculous pneumonia; (2) the acute symptoms may subside and the temperature fall to normal in two or three weeks; (3) it may shift into the ordinary chronic ulcerative type of case.

It is noteworthy that many of these cases present every feature of a lobar pneumonia, and for a week or so no suspicion of the true nature of the trouble occurs. In not a few instances, when it finally becomes apparent that tuberculosis is present, it is said that the latter was a result of pneumonia.

When lobar pneumonia develops as a complication in cases of pulmonary tuberculosis it is often impossible at the onset of the trouble to determine whether the acute disturbance is a true pneumonia or an extension of the tuberculous process. The following cases will serve as illustrations:

A physician with a well-marked but arrested lesion involving the greater part of his right upper lobe was suddenly seized with chilly sensations, vomiting, marked prostration, and a rapid rise of temperature. He had previously been in excellent health, although his sputum always showed the presence of tubercle bacilli. Examination of his chest a few days later revealed a consolidation of his right lower lobe. When I saw him he had been ill twelve days and

the temperature was continuous, varying from 101° to 103° F. He was fearful that he had suffered a relapse. In this case there was nothing to guide one as to whether it was a lobar pneumonia or sudden extension of his tuberculosis. A day later he had a crisis and the lung rapidly cleared up.

Another somewhat remarkable case was that of a woman with moderately advanced lesions in both upper lobes. Her temperature had been normal for two months and she was taking two hours exercise daily. She was seized suddenly with a chill, marked prostration, and a high fever. A few days later involvement of the entire left lower lobe became apparent. She ran a febrile course of ten days, when her temperature reached normal by lysis. Recovery was apparently complete. Ten days later the same phenomena recurred with involvement of the right lower lobe. This attack subsided as the first had done.

These cases differ from the first mentioned group in that the presence of tubercle bacilli offers no aid as they are already present. The *x*-rays are helpful at times, but unfortunately one is often unable to obtain this assistance.

It is interesting to note that even when the lung which is already tuberculous becomes pneumonic, no activity of the tuberculous lesion occurs. This is surprising in view of the fact that ordinary "colds" are so often the means of bringing about a relapse. In this connection it might be noted that typhoid fever, which is so commonly complicated with a bronchitis, is usually well borne by tuberculous patients.

Malignant Disease.—The association of malignant disease of the lungs and tuberculosis is unusual. Indeed, one may go farther and state that a tuberculous individual only infrequently develops malignant disease in any part of his body. Until a few years ago my own experience indicated that the coexistence of these two conditions was a rarity, but I have since had three patients with advanced pulmonary lesions who developed a malignant tumor elsewhere in the body. Among 60 cases of malignant disease studied by Ross there were two cases in which tubercle bacilli were found in the sputum. He notes that the frequency of healed tuberculosis lesions found at the autopsy is of no significance, as they are found with equal frequency in individuals dying of other diseases.

Focal infections offer two problems: First, as to whether a complex of indefinite symptoms is tuberculous in origin. For example, a patient may complain of lassitude, have a slight but persistent fever, loss of weight, and in certain latent sinus infections also have considerable cough. Such cases are often mistaken for tuberculosis and treated as such for some time. It is only when failure to obtain improvement occurs that the suspicion arises that the source of the trouble may be another type of infection. Secondly, a definitely tuberculous individual may fail to improve or may develop what seems to be slight exacerbations of the disease when the trouble is in reality due to an associated focal infection. One should always be alert for such possibilities in cases which fail to improve and for which there is no satisfactory explanation. The trouble may be in the tonsils, carious teeth, etc. I have had several humiliating experiences in this regard. A man under my care had improved very satisfactorily up to a certain point. Then for a period of nearly six months he was subject to recurring attacks of fever, associated with lassitude and some loss of weight. I persisted in ascribing these attacks to his pulmonary lesions. Finally he was given a general overhauling, and a chronic sinus infection was found. This was drained, and he speedily went on to a complete recovery. A chronically diseased tonsil in another case so retarded recovery that nothing was accomplished until the offender was removed; but it took me three months to come to this decision.

Neurasthenia.—As in the case of nearly all the complications mentioned neuras-

thenia presents the problem of differential diagnosis as well as its recognition as a complication.

For some years I have recognized a type of tuberculosis in which the outstanding feature is the combination of symptoms embraced under the term neurasthenia. Such patients often suffer for years from some ill-defined malady; they tire easily, especially at the end of the day, and are extremely susceptible to fatigue on the slightest exertion. The blood-pressure is low or is lowered as the result of exertion. Respiratory symptoms are slight or entirely absent. Recently this type has been described under the term of "masked" or "occult" tuberculosis.

Not infrequently patients with definite clinical tuberculosis suffer in addition from marked nervous symptoms of a neurasthenic nature. In many the nervous manifestations overshadow the pulmonary symptoms. Many such patients are best handled by the neurologist. They require seclusion, prolonged rest, and the general routine known as the Weir Mitchell rest cure. Indeed in Mitchell's original exposition of the rest cure many of his cases were undoubtedly of the masked type, or were frankly tuberculous with marked nervous symptoms.

Finally neurasthenia becomes a problem in many arrested cases. This is notably the case in those in whom the rest treatment has been unduly prolonged. Not infrequently such patients become too self-centered, timid, and unable to do anything. They complain of fatigue after the slightest exertion, and in addition become the victims of all sorts of vague symptoms. In not a few of them it can be said that while their tuberculosis has been arrested their second state is worse than the first, as they become a burden and annoyance to themselves and every one about them. It often takes drastic measures to restore their self-confidence and divert them back into normal channels.

Mental Conditions. — Tuberculosis is often the terminal event in the insane. In most instances poor nutrition and close confinement offer a ready explanation for the development of the disease. There is one type of insanity however in which tuberculosis is believed by some to be the exciting cause—namely, dementia præcox. Some authorities believe this is always the case, others deny any such relationship. My own experience is confined to four cases in which violent mental symptoms developed in young individuals suffering from tuberculosis.

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PNEUMOKONIOSIS AND TUBERCULOSIS

WITH SPECIAL REFERENCE TO BOTH DISEASES IN POTTERS

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Since the time of Ramazzini it has been recognized that dust has been capable of producing changes in the respiratory system. Furthermore, the opinion has prevailed for many years that occupations which exposed the worker to the inhalation of dust were attended by an unduly high incidence of pulmonary tuberculosis. In spite of the fact that certain forms of dust produce as definite and as characteristic changes in the lungs as do bacteria, the disease pneumokoniosis rarely, if ever, figures as such in our morbidity or mortality returns. It is practically always disguised under some other term, as for example, chronic bronchitis, asthma, pleurisy, tuberculosis, etc. There can be no doubt that in a considerable percentage of cases a diagnosis of pulmonary tuberculosis is made when in reality the condition is a pure pneumokoniosis. This is to be ascribed to the fact that the symptoms and physical signs are frequently identical and too much is taken for granted. Repeated sputum examinations are essential, and I know of no other way of definitely determining whether in a given case it is one of uncomplicated pneumokoniosis or there is a superimposed tuberculous infection.

The literature on the subject of pneumokoniosis is enormous but, it must be confessed, much of it is worthless. In the first place, until very recently there was no distinction made as to the effects of different types of dust. The usual classification of dusts was that of organic, inorganic, and mixed, and all were looked upon as being equally harmful. Fortunately, within the past few years the effects of these different types have been more thoroughly studied.

It is now quite generally accepted that organic dusts, such as vegetable or animal fibres, produce no changes in the lungs. Certainly, thus far, pathological proof is wanting. Inorganic dust, on the other hand, does produce characteristic changes, the evolution of which is as definite as any produced by microörganisms. There is ample proof of this.

Mixed dusts which consist of both organic and inorganic material are dangerous in proportion to the amount of inorganic matter, the organic content being of little consequence.

It is with inorganic dust, therefore, that we are chiefly concerned. While any of the inorganic dusts are capable of causing mischief in the lungs, repeated studies have shown that these dusts vary tremendously in the effects that they produce. Thus the power to cause damage ranges from pure silica, the most dangerous of all forms of dust, to the relatively innocuous cement dust. Silica, for example, may bring about a complete crippling of the worker in as brief a period as from two to eight years, if the exposure is sufficiently intense. Coal dust, on the other hand, even with marked exposure, usually takes twenty to thirty years to produce changes sufficient to produce symptoms.

Collis has emphasized this variability of the effects of dust, not only in the production of fibrosis but also in the incidence of an associated tuberculosis. It seems quite clear that a high percentage of cases of silicosis develop tuberculosis; certain other dusts, on the other hand, do not seem to increase the susceptibility, and some indeed are said to act as a preventive of tuberculosis.

Much of our information regarding the incidence of tuberculosis in various industries is open to criticism. For the most part, the data relating to the frequency of tuberculosis in a given industry is obtained in one of two ways: First, the number of deaths occurring in a certain industry is taken as an index as to the harmfulness of the particular employment, and as a result of this many occupations have received a bad name, when as a matter of fact there was nothing in the industry itself to warrant such a deduction. Second, most of the surveys that have been made have followed the plan of making medical examinations of groups of workers, tabulating the defects found, and then assuming that, if there was a high percentage of certain abnormalities, these abnormalities were to be charged against the occupation. For example, several years ago an extensive survey was made of one of the textile trades. Among the defects found with great frequency was pyorrhoea. It was concluded, therefore, that this trade predisposed the workers to pyorrhoea, an assumption that certainly had little to warrant it.

An additional factor that is too often lost sight of is the influence of the trade process. A man in stating his occupation will almost invariably give the general designation, as for example, hatter, potter, etc. In most occupations there is a great diversity of processes. Some of these proc-

esses involve no risk of any kind; in others there may be a distinct industrial hazard. Thus, a man may state that he is employed in a pottery and as a result is usually classed as a potter. Closer questioning as to the particular work he does in the pottery may reveal the fact that he is a decorator or a packer, in neither of which is there any hazard; or he may be a dipper, in which case the risk is that of lead poisoning and not the inhalation of dust; in all other trade processes connected with the manufacture of pottery or sanitary ware dust constitutes a distinct hazard.

Still another factor that is often neglected is a knowledge of exposure to tuberculosis in the home. In any considerable group of workers, no matter what the occupation may be, it will be found that there is evidence of existing cases of tuberculosis in their immediate families. In such cases it would be difficult to state whether the worker became infected because of his occupation or because of exposure to the disease in his home.

Finally it is urged that any study of the influence of occupation on the causation of disease should include a knowledge of the conditions under which the workers live.

This brief outline of some of the factors involved in determining the relationship existing between pneumokoniosis and tuberculosis may be illustrated by an analysis of a group of potters whom I have had under observation. For some years past the Potter's Union has sent many of its members to the White Haven Sanatorium, located in White Haven, Pennsylvania. To date there have been 88 cases, all being sent to the Sanatorium under the belief that they had tuberculosis.

Their respective numbers and *length of employment* were as follows:

6 MONTHS	1–5 YEARS	5–10 YEARS	10–15 YEARS	15–20 YEARS	20–25 YEARS	25–30 YEARS	30–35 YEARS	35–40 YEARS	45–50 YEARS
1	5	8	11	9	7	10	11	13	8

It is known that the type of dust occurring in potteries is not especially irritant and that it takes at least ten years to show any changes. Of this group 6 had been employed five years or less and 8 more ten years or under. It is hardly probable that any of them had received sufficient pulmonary damage to increase their susceptibility to tuberculosis. Certainly, in the case of a man who worked as a potter no longer than one or two years and then showed signs of tuberculosis, the industry could hardly be charged with it.

It should also be noted that 32 of the group had followed the occupation from 30 to 50 years before they manifested any symptoms.

The numbers employed in the several *trade processes* were as follows:

Presser	61	Decorator	2
Jiggerman	9	Dipper	3
Kilnman	9	Packer	1
Saggermaker	1		

Pressers, jiggermen, kilnmen, and saggermakers are all exposed to dust under about the same conditions. Decorators have to do with the ornamentation of chinaware and are not exposed to dust in the slightest. In the case of dippers the hazard is that of lead poisoning; dust is a very minor factor. The one listed as a packer worked in the store room and packed the finished china for shipping.

It will be seen therefore, that 6 of the group designating their trade as that of potter were not exposed to the dust at all and had no opportunity to develop pneumokoniosis. Tuberculosis, therefore, is not to be charged to dust in these cases.

As regards *exposure to tuberculosis* there was a history of exposure in the family in 22 and of exposure elsewhere in 6. In this group of 88 patients 22 stated that some member or members of the immediate family (father, mother, brother or sister) had died of the disease. In 6 more there had been exposure through a tuberculous wife or intimate associate.

In those cases in which it was known that infection existed in the family it would be difficult to fix the source of the infection. To charge it against the industry would be manifestly unfair. To a less extent this is true where the exposure is less intense but still a possible source of the trouble.

Examinations for *tubercle bacilli in the sputum* showed that tubercle bacilli were present in 72 and absent in 16. Although all of these 88 patients were sent to the sanatorium as cases of tuberculosis it was impossible to establish such a diagnosis in 16, or 22.2 per cent. The sputum was repeatedly examined in these cases but tubercle bacilli could never be demonstrated.

It is to be borne in mind that, in the early stages of pneumokoniosis, without an associated tuberculous lesion, the physical signs are practically negative. In the third stage the physical signs are marked and nearly always are not to be distinguished from those found in advanced tuberculosis. Furthermore, it is not always possible, even with the X-rays,

to determine whether the case is one of pneumokoniosis alone or whether there is an associated tuberculous lesion. The examination of the sputum then is our chief reliance in detecting those who have and those who have not tuberculosis. Neglect of this precaution has led to the inclusion in tuberculosis statistics of a fairly high percentage of cases in which extensive fibrosis of the lungs, the result of a pneumokoniosis, is the actual trouble.

TYPE OF TUBERCULOSIS OCCURRING IN POTTERS

Finally, a word as to the type of tuberculosis which as a rule is encountered in this occupation:

When tuberculosis is superimposed on the pneumokoniosis, in most instances it is nontoxic. The constitutional symptoms, such as fever, tachycardia, sweating, etc., are slight and in most instances quickly disappear with rest.

The lack of toxic symptoms is to be ascribed, I believe, to the extensive fibrosis present. This tends to limit the spread of the disease and also to prevent absorption.

It is well known that in cases of tuberculosis in which fibroid tissue forms very slightly or not at all the disease spreads rapidly and toxic symptoms are marked. On the other hand, in chronic cases with marked fibrotic changes the disease is of long duration and toxic symptoms are absent or very slight.

The presence of a marked fibrosis in these cases would seem to argue in favor of its rendering the lungs less susceptible to the tubercle bacillus, rather than increasing the susceptibility. This, indeed, is said to be true of coal dust. This dust is not especially irritating and the fibrosis it gives rise to is very slow in its evolution.

In the case of potters it seems to be true that the tuberculosis is not apt to develop until after many years in the trade and that when it does it is frequently of a latent type.

On the other hand, the evidence that silicosis is, in the great majority of instances associated with tuberculosis, sooner or later, is undoubtedly true.

The reason is not clear. I would advance the following hypothesis: Silica is the most irritant of all dusts and those exposed to it in its pure form are incapacitated in from two to eight years. In other words, it will produce as much damage in this brief period as occurs after thirty

to fifty years in a pottery or in a coal mine. Instead of being a slow chronic process, silicosis is subacute and in some instances distinctly an acute process. It would therefore seem that lungs acutely or subacutely inflamed might readily become a fertile field for the tubercle bacillus.

In conclusion it is to be borne in mind that no dust, not even silica, can cause tuberculosis. It may as in the case of silica, predispose the individual to the disease, but without the presence of the tubercle bacillus tuberculosis cannot develop.

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FURTHER OBSERVATIONS ON THE TREATMENT OF DIABETES AND TUBERCULOSIS[1]

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Several years ago we (1) presented before this association some data with regard to the treatment of diabetes and tuberculosis, when these two diseases are associated in the same patient. An increasing experience has served to emphasize and expand some of the views expressed at that time. The association of these two diseases presents a particularly vicious combination to treat. At the outset one is confronted with the problem of the diet and these questions arise: (1) Should we ignore the diabetes, as was the common practice in the past, and treat the tuberculosis? or (2) Should we ignore the tuberculosis and endeavor to control the diabetes? Before we enter into a discussion of our attitude toward these questions let us consider briefly some elementary concepts of the two diseases.

Diabetes develops, as a rule, in a person who is over weight for his age and height. Diabetes, as Joslin puts it, is often the penalty of obesity, of overeating and underexercising. Diabetics usually have an excellent appetite and good digestion, but an inability to utilize carbohydrates, with the resulting hyperglycemia, glycosuria and other symptoms of the disease. Diabetics also have disordered protein and fat metabolism, and the inevitable result of the uncontrolled disease is wasting, reduced resistance to infection, coma and death.

Pulmonary tuberculosis, on the other hand, develops, as a rule, in those who are under weight for their age and height. Undernourishment and overexercise, that is, faulty dietary factors and fatigue, play important etiological rôles. The appetite and digestion are frequently impaired (2). There is no reduction in the ability to utilize carbohydrates, protein and fat, but the result of uncontrolled tuberculosis is like diabetes in the wasting, weakness and death.

[1] Presented by title before the Clinical Section of the Eighteenth Annual Meeting of the National Tuberculosis Association, Washington, D. C., May 4–6, 1922.

At first glance it would seem rather queer that these two diseases with such diverse origins should ever be associated. It is our belief that they are more commonly associated than is generally considered. The question frequently propounded is: Which disease occurred first in the individual? It is our opinion that in practically all cases diabetes is the initial disorder and the active tuberculosis a subsequent development. Whether a latent tuberculosis is activated by the diabetes, or whether reinfection occurs as a result of disturbed metabolism, does not particularly concern us at this place. It is to the point, however, that the diabetes probably determines in most instances the development of tuberculosis in the person in whom both are found to be present.

If our elementary concepts of the two diseases are correct, it would therefore seem logical to give the treatment of the diabetes our first consideration, applying, at the same time, such measures as rest and fresh air, which are not incompatible with a strict diabetic treatment. Our experience has more than justified the attitude of ignoring, for the time being, the tuberculosis, as far as the diet is concerned, and of attempting to correct the hyperglycemia and render the urine sugar-free by the application of either the fasting method of Allen, of the gradual reduction method of Joslin, or even the high fat and low protein diet of Newburgh and Marsh. The inevitable result of the application of these dietetic restrictions is a loss of weight which to one interested in the tuberculosis is quite disconcerting. A loss of eight or ten pounds is not uncommon. Our reply to those who are concerned with this loss of weight is that it would inevitably occur if the diabetes were not controlled. Following such a loss of weight from treatment, it is possible to have a patient gain in weight to an extent that is not possible in any other way. In other words, following dietetic restrictions, there is a gain in the patient's ability to utilize carbohydrates and properly metabolize fat and proteins, and with this improvement a chance not only for a gain in weight, but an increased resistance to further extension and activity of his tuberculosis. Increased resistance to the progress of the tuberculous infection is a more important result of antidiabetic treatment than ability to gain weight. We are quite convinced, upon more mature reflection, that in that particular group of tuberculous patients in whom diabetes is present, weight increases have less significance, as far as the improvement of the tuberculous condition is concerned, than in others, and this is in keeping with our knowledge of the prognosis of diabetes. The undernourished diabetic keeps well longer than one who tends rapidly

to put on weight. The tuberculosis will improve even though there is no considerable gain in weight, if the diabetes remains under control at a given weight. The following case records are important in this connection:

Case 1. W. J. B., male, aged thirty-one years, referred by Dr. Joseph Walsh of Philadelphia and admitted to the Pennsylvania Hospital, January 12, 1922, and discharged March 30, 1922. *Family History*: Negative. *Past History:* Appendicectomy in 1911. Laparatomy for adhesions in 1913. Influenza in 1918. During 1921 he suffered frequently from painful hemorrhoids. *Present Illness*: Admitted on November 27, 1921, to St. John's Hospital, St. Louis, for operation for hemorrhoids. For three weeks prior to admission he had been annoyed by an "awful thirst" and the passage of much urine. He had also had for some time (he does not know how long) a slight cough with occasional expectoration. He had never had any blood spitting. For about four years he had noticed from time to time annoying pains in the left chest. The urine examination upon admission to the St. Louis hospital showed sugar and the examination of the sputum showed tubercle bacilli. A diagnosis of diabetes and tuberculosis was made and the operation for hemorrhoids postponed. The patient was then referred to Dr. Walsh who confirmed the diagnosis of the two conditions. Dr. Walsh examined the urine upon a number of occasions and found from 5 to $12\frac{1}{2}$ per cent sugar. The patient's best weight was 180 pounds in 1913. From 1913 to October, 1921, he averaged 165 pounds. From October to November 27, 1921, the time of admission to the St. Louis hospital, he lost about 20 pounds, reducing his weight to the lowest level, that is, 145 pounds (the standard for his height, 5 feet $10\frac{3}{4}$ inches at age 31, is about 167 pounds).

Physical Examination: Upon admission to our hospital he was rather pallid and weak and showed signs of slight pulmonary involvement limited to the tops of the lungs. A few scattered râles were found at the right apex, but none on the left side. The heart was normal. The abdomen was normal. The extremities showed nothing abnormal.

Laboratory Studies: Blood chemistry studies revealed the following: Non-protein nitrogen, 40 mgm.; urea nitrogen, 14.3 mgm.; uric acid, 2.5 mgm.; creatinin, 1.4 mgm., and sugar, 250 mgm. per 100 cc. The urine contained approximately 5 per cent of sugar. The Wassermann test was negative.

Progress and Comment. Following three days of restricted diet and a fast of two days he became sugar free. Carbohydrates, proteins and fats were then added gradually from day to day without producing glycosuria, until a maximum of 220 to 230 gm. of carbohydrates, 105 to 110 gm. of fat and 86 gm. of protein were reached about one week before discharge. During this time his

weight remained unchanged, oscillating from 140 to 144 pounds. His temperature remained normal during the entire period of observation except for four or five days when he had an acute cold. He gained remarkably in appearance and in strength. At first placed in bed he was subsequently given graduated exercise, until at the time of discharge he was up and about the greater part of the day and walking several hours. Physical examination upon discharge failed to reveal any moisture at the top of the right lung. We have every reason to believe that, barring accidents, this patient should remain well, especially since he is highly intelligent. While it is true that his pulmonary lesion was relatively insignificant, we feel that if his diabetes had not been promptly controlled, the probabilities are that it might have become a serious affair. During his hospital stay the patient was taught how to examine his own urine and from his own studies while under care had learned food values to the point where he was practically able to select his diet. Since his carbohydrate tolerance had been raised to such a high point, he could do this without the necessity of weighing the articles of food. This patient illustrates how an improvement can be brought about without weight gains.

Case 2. H. R., male, aged fifty-one years, admitted to the Jefferson Hospital Chest Department, November 27, 1921, and discharged February 25, 1922. *Family History*: Negative. *Past History*: He had always enjoyed good health until the onset of the present trouble in September, 1920. He stated, however, that five years ago sugar was accidentally found in his urine during the course of a "health examination." A number of examinations subsequently made showed its continued presence. The patient tried dieting, with and without the advice of physicians, but apparently no serious attempt was made at any time to render the urine sugar free. *Present Illness*: In September, 1920, he caught a severe cold which was followed by cough and expectoration which continued to the time of admission to the hospital. A small hemoptysis occurred in February, 1921. From January to April, 1921, he remained in bed. Between April and November, 1921, when he was admitted to the hospital, he was up and about the house, but unable to do any work. On November 18, 1921, just prior to his admission to the hospital, he had an acute pleurisy. He had received no treatment for the diabetes which had been ignored since the onset of the symptoms referable to the chest. His appetite and digestion have always been good. There has been no noticeable increase in the fluid intake or output. The patient was usually constipated. His best weight was 187 pounds in 1917 and his lowest weight 137 pounds at present. He believes that there was a definite loss of weight before the onset of his chest symptoms, although he doesn't know how much. He stated that he was "fat" in 1917 (the standard for his height and age at that time is 148 pounds).

Physical Examination and Laboratory Studies: A fairly well nourished adult with signs in the chest of moderately advanced disease of both lungs. The sputum was positive for tubercle bacilli, the urine showed 5 per cent, 4 per cent, 4.5 per cent and 5 per cent sugar during the first four days in the hospital. The Wassermann test was negative.

Progress and Comment: The patient was placed at rest in bed and after three days of restricted diet was fasted for two days, when he became sugar free. Carbohydrates, first in the form of green vegetables, coincidentally proteins, and finally fats were added and increased from day to day, always keeping in mind not to exceed the fatty acid-glucose ratio of 1.5 to 1. During the course of one month it was possible to reach a diet consisting of 115 to 120 gm. carbohydrates, 100 to 110 gm. of fat and about 90 gm. of protein, without glycosuria. During the early part of the treatment the weight dropped from 137 pounds to 126 pounds, and then, as he was beginning to gain several pounds, the patient developed an abscess of the chest wall requiring incision. His weight dropped to 120 pounds. Following the incision and drainage of the abscess the weight returned to 125 pounds. Thereafter, from January 2 to February 8, when he left our care against advice, he improved very rapidly as far as both his diabetes and tuberculosis were concerned. He had reached a carbohydrate tolerance of 180 gm. daily. His temperature, which had been oscillating in the vicinity of from 100° and 101°, was practically normal during the last month of observation. His cough and expectoration had greatly improved. The signs in his chest, however, were unchanged. The patient felt so well that he refused to stay in the hospital longer.

Case 3: P. G., female, aged sixteen years, admitted to the Jefferson Hospital Chest Department, September 17, 1921, and continuing under observation (April 15, 1922). *Family History*: Father and mother have tuberculosis; one brother and one sister are in poor health, cause unknown. One brother and three sisters are living and well. *Past History*: Measles in early childhood. Pneumonia in February, 1916. *Present Illness*: About three months after the attack of pneumonia in 1916, from which she had apparently made a very satisfactory recovery, she began to cough, expectorate and lose weight and strength. These symptoms would clear up and return at intervals until February, 1918, when she visited a tuberculosis dispensary where a diagnosis of early, active pulmonary tuberculosis was made. At the same time the Wassermann reaction was found to be 4 plus and the urine was found to contain sugar. She was referred to the Pennsylvania Hospital for treatment, where she was admitted on June 10 and discharged on August 10, 1921, sugar free. Intensive arsphenamine therapy resulted in a negative Wassermann reaction. After her return home several lapses in the diet occurred and glycosuria developed with a return of the cough and weakness. She was admitted to the

Jefferson Hospital Chest Department on September 17, 1921. At this time the glycosuria varied between 1 and 2 per cent and the fasting blood sugar 180 mgm. per 100 cc.

Progress and Comment: The patient was placed at rest in bed and the glycosuria disappeared after a restriction in the diet for several days followed by one day of fasting. By the gradual addition of carbohydrates, proteins and fats, it was possible to obtain eventually a dietary consisting of 125 gm. of fat, 100 gm. protein and from 120 to 125 gm. carbohydrate. The weight upon admission was 99 pounds and after a slight loss there was a gradual gain to 113 pounds and then a drop to 106 pounds, which the patient has maintained on an average to the present time (April 15, 1922). The urine has remained sugar free and after the first month of the hospital stay the cough and expectoration practically disappeared. The temperature has continued normal and physical examination of the lungs reveals no evidence of moisture. The patient is allowed to be up and about the ward and on thirty minutes' walking exercise. The Wassermann reaction continues negative. This patient is particularly interesting, in view of the coexistence of three diseases, early pulmonary tuberculosis, latent syphilis and diabetes mellitus. They were recognized in this sequence by the physicians who saw her. If one can conjecture their order of appearance, it was probably syphilis (there are some features suggesting a congenital infection), diabetes and then tuberculosis. We feel quite certain that the intensive arsphenamine therapy and the antidiabetic treatment have given her the chance to combat the tuberculosis, which to date she seems to be doing satisfactorily.

It is not within the province of this paper to discuss the details of the dietetic management of diabetes, since the work of Joslin, Allen and others has made this a matter of common knowledge. There is a feeling, however, among some sanatorium workers, that such treatment is not satisfactory or possible unless an elaborate equipment and a trained dietitian are available. We have found it entirely feasible where first, the physician is willing to give the intensive supervision necessary and second, the individual who prepares the food, whether a dietitian, so called or not, is willing to coöperate, and manifests an ordinary intelligence in the use of the Joslin food tables and the gram scales. After all, the interest of the physician in charge is the important factor in the success of the treatment.

It may not be remiss to speak a few words in regard to acidosis. We have never seen acidosis develop in a diabetic with tuberculosis under treatment when attention was paid to the proper adjustment of the carbohydrate, fat and protein of the diet. Those patients whom we have

seen with acidosis had either not received any treatment before coming under observation, as was the case of one patient who died within a week after admission to the White Haven Sanatorium, with severe diabetes and hopelessly advanced tuberculosis, or else had failed to follow treatment while under observation or after leaving institutional care. A certain number of cases resulted from the attempt to push the fat in the effort to raise the calory value of the diet. The fats are particularly dangerous. On the other hand, a certain amount of fat in the diet is necessary if the catabolism of the body fats is to be prevented. Woodyatt (3) has recently insisted upon this and points out that unless the diabetic is obese, complete fasting is undesirable for desugarizing, because it compels him to draw fat from his tissues. He states that the practice of starving, or virtually starving, a patient in order to render his urine sugar "free," and then building up the diet, first with carbohydrate and then with protein, with particular avoidance of fat, would appear to be based on the supposition that if fat were administered it would increase the catabolism of fat. Such a procedure disregards the endogenous food supply, and illustrates the necessity of thinking in terms of the metabolism rather than of the diet.

The important point in regard to the fats, therefore, is to know how to adjust the diet so that a maximum of fat may be given without disturbing the fat metabolism, with the resulting formation of ketogenic substances and acidosis. As Woodyatt points out, all the foods which enter the body resolve themselves into either fatty acid or glucose. When acidosis develops it is the result of an imperfect oxidization of certain fatty acids as the result of the absence of a sufficient amount of oxidizing glucose. The ratio between fatty acids and glucose should not exceed 1.5 to 1. It follows, therefore, to quote Woodyatt,

> that the rationale of dietetic management in diabetes is to bring the quantity of glucose entering the metabolism from all sources below the quantity that can be utilized without abnormal waste; and to adjust the supply of fatty acids in relationship to the quantity of glucose so that in the mixture of food stuffs oxidizing in the body, the ratio of the ketogenic fatty acids to glucose shall not exceed limits compatible with freedom from ketonuria. When, as, and if, under these conditions of relative rest for the pancreas, the glucose using function improves, then the food supply may be increased gradually in so far as this can be done without disturbing the above relations.

It is of first importance, therefore, to know that a given quantity of carbohydrate yields in the body 100 per cent glucose and no fatty acid,

protein yields 58 per cent glucose and 46 per cent fatty acid, and fat yields 10 per cent glucose and 90 per cent fatty acid. With this information it is possible to calculate the diet, so that the ratio of fatty acids to glucose of 1.5 to 1 is not exceeded.

The determination of the glucose tolerance, or the amount of glucose which the body is able to utilize, is of the first importance in the effort to ascertain an optimal diet for a given individual. Heretofore it has been the practice to add small quantities of carbohydrate from day to day until sugar appeared in the urine. This is a slow method and it has been superseded by what is known as Woodyatt's optimal diabetic diet. For information as to the rapid estimation of this diet, the reader is referred to the recent article by O'Hara (4), which also includes a convenient chart.

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SYPHILIS OF THE LUNGS SIMULATING TUBERCULOSIS.

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Syphilis of the lungs is considered a very rare condition, especially that of the acquired type. This latter type manifests itself in three forms; diffused gummata, fibroid induration originating usually at the hilus of the lung, and consolidation and catarrh. The last form may occur at the root of the lung or at the apex (1).

In 1915 H. R. M. Landis and Paul A. Lewis, of the Henry Phipps Institute, called attention to the fact that latent syphilis of the apex of the lung was probably more frequent than usually regarded (2). They reported five cases which had come under their notice, each having many physical signs and symptoms of tuberculosis, except that the tubercle bacillus was absent from the sputum. These cases had been treated as tuberculosis without permanent improvement. Positive Wassermann reactions were afterwards obtained and after antisyphilitic treatment the symptoms in each case were entirely relieved.

In the one clinic of the Phipps Institute which has been under my care, I have noted cases which to the casual observer might have been diagnosed as pulmonary tuberculosis, but, after investigation, have proved to be syphilis of the lungs. For illustration I have selected three typical cases which, I feel, will show their character.

Case I.—18950 Phipps Institute. In January

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1919, a man, aged forty-three, unmarried, a railroad employee, was referred to us by a physician with a provisional diagnosis of pulmonary tuberculosis. This man had previously consulted another physician who also had made a diagnosis of tuberculosis. He gave a history of having had a cough for three years, most severe at night, with white sputum for the same length of time. He had occasionl hoarseness, but had never had blood tinged sputum or night sweats. He had had pain over the liver during this period. In 1915 he weighed 202 pounds, while his present weight was 161. As to his family history, his father died in 1887 of tuberculosis. He admitted an initial luetic lesion in 1892.

Examination of the heart showed the presence of a systolic murmur at the second cartilage on the right side, the second heart sound heard in that area being bell like.

Examination of the chest showed it to be well filled in, and expansion to be good and equal. Percussion gave an impaired note over the apex anteriorly and posteriorly. On auscultation broncho-vesicular breathing was noted over this area in front, and slight bronchovesicular posteriorly. Increased vocal resonance was noted also over the right apex. The only râles noted were at the base of the right lower lobe. The sputum was negative.

The fact that this patient gave a positive history of an initial lesion, that he had a pain referred to the liver, a possible perihepatitis, that he had aortitis, made us suspicious that he was suffering from syphilis of the lungs and not pulmonary tuberculosis. It was requested that a Wassermann test be made, and the result was a four plus reaction.

For a period extending over a year he was given antisyphilitic treatment, consisting of injections of salvarsan at first, with internal medication of mercury and potassium iodide afterwards. As a result his cough has been relieved and his weight at the present time is 180 pounds.

Case II.—No. 20751 Phipps Institute. A married woman, forty years of age, came to us about five months ago. Her family history showed that her father had died in 1910 of tuberculosis, and her maternal grandmother had died of a pulmonary hemorrhage. She gave a doubtful history of pleurisy, but denied having had syphilis. She had used alcohol excessively in former years. She stated that her husband suffered from headaches. Her chief complaint was a cough of four months duration, with a very large amount of white sputum. She had never had blood tinged sputum, but had had night sweats during this period. She had also had hoarseness and dyspnea, and her menses had been suppressed for four months until three weeks before, when she menstruated profusely for three days. A year and a half before the date of her entrance into the clinic she weighed 142 pounds, at this time she weighed eighty-nine pounds.

Examination of the chest showed it to be flat, with a moderate depression above the right clavicle. There was an impairment of resonance over the entire upper right lobe, and over the apex of the upper left lobe to the level of the second rib, anteriorly. Posteriorly there was impairment over both apices. Bronchovesicular breathing was heard over these areas, and a few râles were noted over the right apex in front, and over both apices in the back. The heart was negative. Her pulse was 104 and her temperature was 99.2°.

However, the sputum was negative as to tubercle bacilli, and a Wassermann was requested, which resulted in a four plus reaction. At the time of the next visit to the dispensary and before a report of the Wassermann had been received, the patient had been spitting blood tinged sputum, and was having sweats every night. She had lost one and a quarter pounds in weight.

After we were assured that she was suffering

from lues, we advised the patient to take salvarsan injections in our syphilis department. On account of some prejudice to this form of treatment she refused to attend the genitourinary clinic, and would return to the institute only upon our promise that she would be treated by internal medication and not by injections. Consequently she was placed upon mercury and potassium iodide in graduated doses.

Until six weeks ago she came to the clinic regularly. For a period of two weeks during the time of her attendance she had no cough at all. The hemoptysis and the sweats were entirely relieved. She had just returned to the clinic with a moderate cough, but no blood spitting or sweats. She had, however, a continuous headache. Her weight at the time of her last visit was 124 pounds.

Case III.—No. 18544. An unmarried man, thirty-five years of age, came to the clinic in 1918 with a history of having had a productive cough from time to time for the past five years. He had had dyspnea for two weeks, a poor appetite for the same length of time, with nausea and vomiting after meals.

His family history was negative, but he admitted having been an excessive user of alcohol until 1917. He had pneumonia and pleurisy in 1908, typhoid in 1889, influenza in 1917, and so-called stiff joints three and a half months before. He gave a doubtful history of a primary luetic lesion in 1918, the same year in which he came to the clinic. He had not had blood spitting or night sweats, but during the previous four months had lost thirty-nine pounds, his weight at this time being 86 pounds. His finger nails were slightly curved. There was some discrepancy between the history of a possible primary luetic lesion a few months previously and of a cough of five years' duration, if we were to presume that the cough was of syphilitic origin.

On inspection it was noted that he was poorly nourished and his chest was poorly developed. On the right side there was a moderate depression above the clavicle and flatness below. Expansion was poor during inspiration. Upon percussion an impairment of resonance was noted over the right apex, and a slight impairment over the left, anteriorly and posteriorly. Upon auscultation there was weak breathing over the entire lung, bronchovesicular in front over the apices, weak vesicular over the left apex and granular over the right apex posteriorly. Increased vocal resonance was noted over both apices, front and back. The sputum was negative, but the Wassermann test was four plus. Dr. Kaufman, of the Phipps Institute, has called my attention to the frequency of weak breathing in these cases which give positive Wassermann reactions.

Four months of antisyphilitic treatment, although irregularly given on account of the failure of the patient to put in appearance, modified favorably all of his symptoms. At the time of his last visit his cough had almost entirely disappeared and his weight had increased twenty-eight pounds.

Collectively, these patients gave all of the cardinal symptoms and signs of tuberculosis; prolonged cough, expectoration, blood tinged sputum, hoarseness, night sweats, dyspnea, gastric derangement, amenorrhea, marked loss of weight, curved nails, slight elevation of temperature and increased pulse rate, flat chest and unilateral lagging on respiration, together with impairment of resonance over the apices, bronchovesicular and granular breathing, increased vocal resonance and râles. Yet it seems satisfactorily proven by laboratory and therapeutic tests that their lesions were of syphilitic origin. It may occur to some that we were dealing with tuberculosis complicated by lues, and by a relief of the baneful influence of the latter disease upon the former, the condition of the patient was

improved. However, it is more than probable that any case of tuberculosis giving the signs and symptoms recorded in these cases would produce tubercle bacilli in the sputum.

CONCLUSIONS.

The frequency with which these cases appear at the Phipps Institute causes us to conclude first, that syphilis of the apices of the lungs is not by any means a rare condition, and that there are many cases of this disease being treated for pulmonary tuberculosis. Second, that we should avail ourselves more frequently of Wassermann and other blood tests in private practice in cases giving signs and symptoms of active tuberculosis, but not giving positive sputum. This should be done whether a history of a primary luetic lesion is obtainable or not, realizing that syphilis is often innocently acquired. Signs of an aortitis, of a perihepatitis, of weak or suppressed breath sounds, should make us suspect syphilitic infection. By pursuing such a practice there is no doubt that we will arrest some cases which are running a rapidly downward course.

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CHAULMOOGRA OIL IN THE TREATMENT OF TUBERCULOUS LARYNGITIS

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Chaulmoogra oil has been used with considerable success in the treatment of leprosy, and recently experiments have been made on tuberculous animals; but to the best of my knowledge, it has not been tried on the laryngeal lesions of human subjects. My attention was first called to this oil as a possible remedy in the treatment of tuberculous laryngitis by Dr. John I. Fanz.

Chaulmoogra oil treatment was begun, Feb. 4, 1921, at the Department for Diseases of the Chest of the Jefferson Hospital and at the Henry Phipps Institute of the University of Pennsylvania. This report gives the results of sixty cases treated over a period of eight months. The treatment has been conducted more to learn the effects on the pathologic lesions of the larynx and the symptoms than on the tubercle bacillus itself, for laboratory studies have shown that this oil is not a tubercle bacillicide.

Chaulmoogra oil gave promising results from the beginning in cases in which there were dysphagia and pain in the throat. Other oils used proved simply emollient; while chaulmoogra oil, in the majority of cases, exerted an analgesic action on the larynx which became more complete after repeated treatments. While improvement in the lesions is slower than was hoped for, yet cases treated with chaulmoogra oil have responded as rapidly as those treated with other drugs, and the treatment is much more easily borne. Preliminary cocainization has not been necessary, and there has been no pain or discomfort in the throat afterward, but rather a pleasing sensation of warmth in the throat and chest. In the cases in which intratracheal injec-

tions were made, sputum was rendered more fluid and was expelled with greater ease. Dryness of the throat, which frequently is present in tuberculous laryngitis, was improved but slightly in the majority of cases.

At first the oil was applied by means of a cotton tipped applicator saturated with a 10 per cent. solution in liquid petrolatum directly to the laryngeal surface. Following this there was no pain or discomfort except a slight momentary cough. Later the strength was increased rapidly up to the pure drug.

Chaulmoogra oil works best by intratracheal and intralaryngeal injection. One cubic centimeter of the oil, of the strength desired, usually 10 or 20 per cent. in liquid petrolatum or olive oil, is drawn up in a Luer syringe armed with a metal eustachian catheter. While the patient holds the tip of the tongue, wrapped in a paper napkin, between the index finger and the thumb of the right hand, the syringe tip is introduced, guided by the throat mirror, into the pharynx (not the larynx) above and behind the epiglottis, care being taken not to touch any portion of the mouth or throat. Two thirds of the contents of the syringe is discharged, drop by drop, into the trachea while the patient breathes quietly. The remainder is then dropped on the cords while the patient phonates. In this way, cough following injection is very slight and often absent. When present, it occurs within five minutes after the injection and lasts for a minute or two.

REPORT OF CASES

The two cases here reported are fairly typical as to results, and are cited because the laryngeal lesions were extensive, and prognosis for a cure and for relief from dysphagia was very unfavorable.

CASE 1.—A man, aged 58, complained of severe cough, marked hoarseness and pain on swallowing, especially for liquids. Physical examination revealed advanced pulmonary tuberculosis. The sputum contained tubercle bacilli; the Wassermann test was negative. The epiglottis was negative; the vocal cords ulcerated in the posterior two thirds; there were marked infiltration and extensive shallow ulceration of the ventricular bands; the interarytenoid fold was thickened and covered with large papillary excrescences; the arytenoids were infiltrated and about three times their natural size. The patient was bedfast.

Treatment from Sept. 20, 1920, to Jan. 31, 1921, consisted of applications of formaldehyd solution and lactic acid in ascending strengths, iodoform, iodin in glycerin, and argyrol. The tuberculous outgrowths on the interarytenoid fold were removed twice with a laryngeal punch, but recurred both times. Improvement was very slight. When the chaulmoogra oil treatment was started, February 4, subjective symptoms were relieved almost at once. The distressing cough, due to the difficulty in raising tenacious sputum, was relieved after the first treatment and the sputum rendered more fluid. In less than a week the pain was gone and has never recurred. In three months' time the ulcerations disappeared. The vegetations on the interarytenoid fold slowly diminished in size and finally disappeared, until at the present time the infiltrated tissues are greatly reduced in size and the mucosa is smooth and clean. Hoarseness is still present, but greatly improved. The patient left the hospital three months ago and is being treated twice a week in the dispensary, practically an arrested case.

The second case illustrates the chief value of the oil, namely, relief of dysphagia.

Case 2.—A woman, aged 34, complained of constant pain in the throat and excruciating dysphagia. Physical examination revealed far advanced pulmonary tuberculosis. The sputum contained tubercle bacilli; the Wassermann test was negative. The lesions in the larynx were most marked on the epiglottis and the arytenoids. The interior of the larynx could not be observed because of the size of the epiglottis, which was of the turban variety with a large ulceration extending backward and involving the left arytenoid. Prognosis for a cure (pulmonary) was hopeless, and the most we could hope for was to relieve the pain and dysphagia, which began in December, 1920. The patient was admitted to the hospital dispensary, Jan. 14, 1921. Local applications of the usual drugs were made, and anesthetic lozenges were used. Improvement was unappreciable, the pain and dysphagia remaining the same. February 8, 5 per cent. chaulmoogra oil in liquid petrolatum was applied locally to the larynx. Three days later, the patient could swallow more easily, although the constant pain still remained. Thirteen days after the initial treatment the pain and dysphagia were so much improved that she was eating and relishing her meals. One month later pain, dysphagia and dryness of the throat were absent. Neither cocain nor morphin was used at any time. By the middle of March, the interior of the larynx could be seen, showing marked infiltrations of the ventricular bands and the interarytenoid fold; the ulcerations on these structures were very shallow. Edema of the epiglottis was greatly reduced, although the large ulceration, while healthier in appearance, was still of a fairly good size. There had been a

slight gain in weight. Cough was less and the sputum reduced in quantity and very easily raised. Later she developed a large superficial ulceration of the pharynx involving the right tonsil and the right side of the uvula, which has proved rebellious to treatment. The laryngeal lesions, after reaching a certain point, remained stationary for a time, while the pulmonary condition became more grave. The arrest of improvement was attributed in part to the beginning of pregnancy with associated gastric disturbances. At the present time the patient is losing ground, although the laryngeal lesions remain almost stationary.

Considering the extent, severity and location of the throat and laryngeal lesions, it is remarkable that pain and dysphagia have been abolished. Chaulmoogra oil has been used three times a week, and occasionally a period of four to six days elapsed between treatments, but at no time did pain or dysphagia return.

CONCLUSIONS

1. The chief value of chaulmoogra oil is in the relief of pain and dysphagia.
2. The relief is continuous, in contradistinction to that produced by cocain.
3. The treatment is not unpleasant or distressing, is without untoward reactions in the larynx, and can be used without previous cocainization.
4. Improvement, while not all that could be desired, seems better than that obtained with other drugs.

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THE DIAGNOSIS OF PULMONARY TUBERCULOSIS FROM THE STANDPOINT OF THE INDUSTRIAL PHYSICIAN[1]

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The early recognition of pulmonary tuberculosis in members of industrial bodies is of the greatest possible moment to the employee himself, his fellow workmen, and his employer. A careful consideration of the method to be employed in the detection of these cases cannot help being of general interest; especially as the views on this subject held by those interested in industrial medicine are by no means uniform.

The early detection of tuberculosis in industrial workers has been recognized as a valuable measure in the prevention of the disease, Sawyer (*Jour. Amer. Med. Assoc., October 16, 1920, lxxv, 1041*) in his article on *Industrial Epidemiology* expressing this very general opinion when he states, "Complete and careful physical examination of all new employees, with periodic reëxaminations when indicated, cannot fail to help in the crusade against this disease" (tuberculosis).

The method to be employed in the detection of these cases in the early stages varies with different investigators, the difference of opinion being chiefly centered in the question of reëxamination; whether it is necessary to reëxamine all the workers at stated periods or only those in whom there seems to be some indication or reason to suspect the presence of the disease. One of the first plans proposed was described by Sachs (*Examination of Employees for Tuberculosis, Committee on Factories, Chicago Tuberculosis Institute, 1912*). This was based upon the examination of all "suspects," the cases being selected on account of (1) their history of having had the disease previously; (2) being in poor general condition or having suspicious symptoms; (3) having histories of protracted cough and expectoration; or (4) having had a death from, or case of tuberculosis in their family or home. This plan of examining only a limited group was recommended for adoption because of the economy of its administration as compared with the periodic examination of the entire

[1] Read before the Section on Medicine of the New York Academy of Medicine, December 20, 1921.

force and hence the greater possibility of its general acceptance. It will be noted that while he appears to consider the periodic examinations of the entire force as the most effective means for the early recognition of tuberculosis, Sachs proposes the plan for the examination of suspects on the grounds of expediency, at a time when the employer had not been educated in regard to the value of health service; or, to be more accurate, when he had not discovered the economic value of this work. This plan was adopted at that time by a number of large corporations, including the International Harvester Co., Montgomery, Ward and Co., the Chicago Telephone Co., and Swift and Co., and a similar plan was employed by Harry E. Mock in the Sears, Roebuck and Co. plant in Chicago (*An Efficient System of Medical Examination of Employees, Trans. Nat. Assoc. for the Study and Prevention of Tuberculosis, 1914*).

While this plan of examining selected cases might have been considered expedient in the days before employers had awakened to the tremendous possibilities of health examinations, it would appear as being incomplete and inefficient when compared to periodic examinations of the entire force combined with entrance examinations. This would seem to be borne out by a careful analysis of Mock's results of five years' experience with the "selective" method from 1909 to 1913, during which time there was a decrease in the proportion of tuberculous cases *among those examined* from 5.64 per cent to 3.55 per cent (5.62, 5.58, 2.37, 3.72, and 3.55 per cent respectively, with an average of 4.01 per cent). Upon these figures he based his statement that his plan was "a comprehensive, yet workable system," leading one to infer that by this method practically all of the cases of tuberculosis were discovered, thus causing a gradual decrease in the incidence of this disease among the employees. If one, however, compares the number of cases of tuberculosis discovered each year with the *number of employees for that year, and not with the number examined*, we find the tuberculosis rates are 0.57, 0.78, 0.26, 0.41 and 0.87 per cent for the five years respectively, with an average of 0.59 per cent. It will be seen that the total tuberculosis rate is higher in 1913 than in 1909, which would not appear to support the view that tuberculosis was being decreased by this method of detection. The average of 0.59 per cent would also appear to be rather low for a large industrial organization, as Mock (*Industrial Medicine and Surgery, 1919, p. 365*) gives for "Tuberculosis, active," the following rates in the four groups which he cites: 1.7 per cent, 0.92 per cent, 3.00 per cent and 1.40 per cent; average, 1.775 per cent, the first group (1.7 per cent) being his own figures.

The examination of 19.932 employees in 154 factories and workshops by Robinson and Wilson (*U.S. Pub. Health Service, Pub. Health Bull., no. 73, 1916*) showed an incidence of 1.1 per cent (220 cases) for tuberculosis. Among the drafted men in the state of Pennsylvania the rate for tuberculosis (excluding suspected tuberculosis) was 1.875 per cent (*Defects Found in Drafted Men, War Dep't. Washington, D.C., 1920*). In our examination of the 5706 police and firemen of the City of Philadelphia we found an incidence rate between 0.84 and 1.43 per cent.

It would appear from the tuberculosis rates just quoted that Mock's figures were well below those obtained in other industrial surveys and that the method he employed was probably responsible for his not detecting all the cases of tuberculosis, unless he was dealing with an unusually healthy group.

Nearly every writer on industrial health matters to-day emphasizes the value of entrance examinations, with periodic reëxaminations, as a means of detecting beginning disease, and they are becoming more and more generally employed. There are unfortunately many diseases so insidious in onset that they become definitely advanced, frequently beyond hope of absolute cure, before the affected person has awakened to the fact that he requires medical attention. This is especially true of pulmonary tuberculosis, a disease which is definitely curable in the large majority of cases when detected in its early stages, with the loss of only a relatively short period of time. When not discovered until well developed the disease requires a considerable loss of time for its arrest and, even with the best results obtainable, frequently entails a loss of working capacity. While many advanced cases may secure an arrest of the disease it is usually only after a very prolonged course of treatment and frequently with an almost total loss of working capacity.

Granting the importance of the early recognition of pulmonary tuberculosis and the value of the periodic health examinations for its detection, the medical examiner is still faced with the difficult problem of what physical signs and symptoms may be accepted as positive evidence of the disease. In the examination of large bodies of men the factor of time is an extremely important one, being usually at the expense of the employer and adding to the cost of the examination. A careful physical examination for pulmonary tuberculosis requires considerable time and is prohibitory in every person examined in the large majority of health surveys.

It would add to the value and decrease the cost of such a survey if some method of selection could be devised, whereby the intensive study for

the detection of this disease need be applied in only those cases in which there are peculiar or special indications of the disease of a general character and recognizable by some easily applied method of study other than physical examination of the chest.

With the hope of developing some such plan of selection we felt that it might prove of value to study the findings in regard to tuberculosis obtained in a general health survey of the police and firemen of the city of Philadelphia recently conducted by the Henry Phipps Institute of the University of Pennsylvania.

This study was made with the object of (1) determining the incidence of physical defects among these men; (2) the obtaining of information as to the value of a general health survey as a means of detecting disease; and (3) the securing of data in regard to the most effective method of conducting such an examination, time required, cost, etc. The Institute was desirous of obtaining this information to assist it in the establishment of a department to provide general health examinations for industrial plants in and about the city of Philadelphia.

A complete general physical examination was made of every member of the police and fire departments, including a study of the height, weight, temperature, pulse, eyes, ears, nose, throat, teeth, skin, genitalia, inguinal rings, deformities and defects, blood pressure, heart and lungs, etc. The routine examinations were performed by Drs. W. R. Gilmour, H. F. Keating, and J. S. Scouller, under the direction of the writer of this article, acting as physician-in-charge. The examination was conducted in such a way that all men found to be normal or with only slight defects were at once returned to duty, but all those in whom serious defects were detected or suspected were referred to the physician-in-charge for reëxamination, and for special examinations, such as Wassermann tests, X-ray examinations, electrocardiographic studies, etc., either directly or in coöperation with Dr. Hubley R. Owen, Chief Surgeon of the police and fire departments. The urine was examined in all cases in which the blood pressure was 150 mm. Hg. or over, or in which there was some clinical evidence indicating the advisability of such a study.

The problem for the industrial physician is very much the same as that for the army examiner, the object being to select those cases in which there is active tuberculosis at the present time and those in which, in his opinion, there is a probability of an old quiescent process becoming active under unfavorable circumstances. He is not especially concerned with the selection of those who have at one time been infected with the

tubercle bacillus or even those in whom actual disease may at some time have been present, provided he can feel reasonably certain that there is little likelihood of the lesion again becoming active. The distinction between infection and disease is extremely important, and frequently an extremely difficult one to make. Every one who has had the opportunity of carefully examining the lungs of a large number of people cannot help having been impressed with the large number of cases encountered in which the physical signs at one apex (usually the right apex) indicate slight contraction of the lung at that point, with possibly some increase in density. These signs are frequently encountered in men who are in perfect health, and in whom a carefully elicited history will reveal no record of illness suggestive of previous attacks of tuberculosis. It would be obviously unjust to consider these persons cases of pulmonary tuberculosis.

Upon what basis would one be justified in making a diagnosis of tuberculosis, either active or inactive, in an industrial health survey?

The answer to this question has been outlined by the Diagnostic Standards Committee of the National Tuberculosis Association in cooperation with the representatives of the Community Health and Tuberculosis Demonstration in Framingham, Massachusetts, in a set of diagnostic standards for the diagnosis of pulmonary tuberculosis in adults with negative sputum (*Diagnostic Standards, Community Health and Tuberculosis Demonstration of the National Tuberculosis Association, Framingham, Mass., 3rd edition, September, 1918*). From their list of minimum diagnostic standards we quote the following first two paragraphs:

1. When constitutional signs and symptoms and definite past history are absent or nearly so, there should be demanded definite signs in the lungs, including persistent râles at one or both apices. By "persistent" it is meant that the râles must be present after cough at two or more examinations, the patient having been under observation at least one month.

2. In the presence of constitutional signs and symptoms, such as loss of weight and strength, etc., as defined above, there should be demanded some abnormality in the lungs, but not necessarily râles.

By "loss of weight" should be understood an unexplained loss of at least 5 per cent below normal limits for that particular individual within four months.

It will be noted that considerable stress is laid upon the importance of constitutional signs and symptoms, and upon the past history of the patient. There can be no question about the value of a complete and

carefully recorded history of the patient in the establishment of a diagnosis of pulmonary tuberculosis and in the determination of the presence of activity of the process.

In the examination of large bodies of men it is seldom possible to secure a history of previous illness in every case reporting for examination. The recording of a history requires considerable time and is valueless unless taken by an experienced person. It is also questionable whether much reliance could be placed upon the facts obtained in a history of the previous illness of men reporting for examination in a large industrial plant. Under such circumstances the diagnosis must rest almost entirely upon the data obtained at the examination itself, although many difficulties attend the establishment of a definite diagnosis of tuberculosis upon the basis of physical signs alone, a problem which has been excellently presented by Hamman (*Penna. Med. Jour., March, 1919, p. 353*) in his article on *Physical Examination in the Diagnosis of Early Pulmonary Tuberculosis.*

The examination of the police and firemen was conducted in such a manner that the "record of previous illness" was not available in every instance, many of the cards not being received until the examination was completed. The record of "previous illness" merely showed the number of times the man had reported to the chief surgeon for injury or disease, the character of the disability, and the length of time the man was off duty. The diagnosis in the large majority of our cases rested entirely upon the physical signs and such additional data as weight, pulse, temperature, blood pressure, etc. Under these circumstances the number of tuberculous persons was probably less than might otherwise have been the case and probably accounts for the large number of instances in which the diagnosis was not absolutely established. We were unable to apply to our cases the minimum standards as laid down by the National Association, our opinion being based solely upon all the data obtainable in each individual case. In many instances the X-rays were employed in questionable cases, this examination being made by Dr. Alfred S. Doyle, assistant to Dr. H. K. Pancoast, Roentgenologist of the University Hospital, University of Pennsylvania.

The attempt has been made in the study of the following tables to analyze the results of our examination and to see whether the various methods of examination, other than the physical examination of the patient, are of any value in the selection of cases for intensive study, and what additional help they may give in establishing the diagnosis.

This is not to be construed as suggesting that only certain persons should receive a careful examination of the chest, but that there are some cases which should receive a more exhaustive, complete and careful study than is usually possible to apply to every member of a large industrial group.

The cases discovered have been arbitrarily divided into groups, being roughly graded according to the degree of positiveness of the diagnosis, as follows:

Group I: Suspected tuberculosis
Group II: Possible tuberculosis
Group III: Probable tuberculosis
Group IV: Arrested tuberculosis
Group V: Definite tuberculosis

We regret that for the purposes of our study we have felt obliged to use a classification which is different from that usually employed, namely, the standard classification of the National Tuberculosis Association, which is so well adapted to the clinical study of tuberculosis. The standard classification is not so well suited to the cases encountered in large industrial groups, where one is not interested in whether they are incipient, moderately advanced or far advanced, or whether they have one, two or three lobes involved, but whether they have actual disesase at the present time which would render them a danger to their fellow workman or the performance of work would be a danger to themselves, or whether they have some indications which would suggest that they would develop actual disease if permitted to perform work of certain kinds or any kind. We have felt that the grouping we have employed indicates the desired information as well as any that could be devised.

We have not included among our cases any of that relatively large group apparently in perfect health, in which are found more or less definite impairment at one apex, with slight bronchovesicular breathing and increased voice sounds. These cases have been grouped separately under the headings "Slight Fibrosis" and "Fibrosis," according to the degree and extent of the signs present, and have not been considered in the present article. It is possible that owing to the conditions under which the examinations were made some of the cases of "Fibrosis" should have been included among the tuberculous, and all of them should be reëxamined from time to time in order to detect any evidence of beginning disease.

Groups I and II include the cases in which there existed some doubt as to the accuracy of the diagnosis; group III, those in which the diag-

nosis was very likely; and groups IV and V, those in which the diagnosis was positively established. The factors which might be of assistance in confirming the diagnosis, which will be considered in detail, are (1) weight, (2) temperature, (3) pulse rate, and (4) blood pressure.

LOSS OF WEIGHT

The National Tuberculosis Association in its pamphlet on Diagnostic Standards, to which reference has been made, defines loss of weight as "an unexplained loss of at least 5 per cent below normal for that particular individual within four months' time." In the present study we were unable to determine the loss of weight in such detail as would determine when the loss of weight had occurred or whether the person had always been below weight. The term "loss of weight" as employed in the present article, therefore, does not conform with the National Association standard.

Loss of weight has always been considered a symptom of considerable significance in the clinical diagnosis of pulmonary tuberculosis, and it therefore is not surprising that it was noted in 116 of the 132 cases of tuberculosis which form the basis of the present study, or 87.8 per cent (table 1). It will be noted that the "arrested" cases, group IV, show the largest proportion of men over weight. The percentage of men under weight varies considerably in the different groups, bearing no constant relation to the degree of certainty of the diagnosis.

It would appear from our study that loss of weight is an extremely common symptom of pulmonary tuberculosis, but that its absence does not by any means exclude the possibility of this disease being present, as 12.0 per cent of the cases discovered were either of normal or over weight.

The proportion of cases over and under weight is given in more detail in table 2, where it will be noted that extreme underweight (20 per cent or over) was a very uncommon finding, being present in only 6 of 132, or 4.5 per cent of the cases discovered.

In computing the percentages of over and underweight each case was considered separately and the actual weight compared to the normal average weight for an individual of his age and height.

The average loss of weight, expressed in terms of pounds avoirdupois, in the different groups (table 3) varied between 11.8 and 21.6 pounds. The net loss of weight in the various groups ranged from 2.2 pounds (arrested tuberculosis, group IV) to 18.3 pounds (probable tuberculosis,

TABLE 1

Percentage overweight and underweight

Summary

	SUSPECTS		POSSIBLE TUBERCULOSIS		PROBABLE TUBERCULOSIS		ARRESTED TUBERCULOSIS		DEFINITE TUBERCULOSIS		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Overweight	3	10.3	0	0.0	2	8.3	5	50.0	5	10.4	15	11.3
Normal	0	0.0	0	0.0	1	4.1	0	0	0	0	1	0.7
Underweight	26	89.6	21	100.0	21	87.5	5	50.0	43	89.5	116	87.8
Total	29	99.9	21	100.0	24	99.9	10	100.0	48	99.9	132	99.8

TABLE 2

Percentage overweight and underweight

	SUSPECTS		POSSIBLE TUBERCULOSIS		PROBABLE TUBERCULOSIS		ARRESTED TUBERCULOSIS		DEFINITE TUBERCULOSIS		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Overweight, 20 % and over	0	0	0	0	0	0	0	0	1	2.0	1	0.7
Overweight, 10–19 %	1	3.4	0	0.0	0	0.0	2	20.0	0	0.0	3	2.2
Overweight, under 10 %	2	6.9	0	0	2	8.3	3	30.0	4	8.3	11	8.3
Normal weight	0	0	0	0	1	4.1	0	0	0	0	1	0.7
Underweight, under 10 %	20	69.0	9	42.8	6	25.0	3	30.0	14	29.1	52	39.4
Underweight, 10–19 %	6	20.6	11	52.3	13	54.1	2	20.0	26	54.1	58	43.9
Underweight, 20 % and over	0	0	1	4.7	2	8.3	0	0	3	6.2	6	4.5
Total	29	99.9	21	99.8	24	99.8	10	100.0	48	99.7	132	99.7

TABLE 3

Overweight and underweight expressed in pounds avoirdupois

Police and firemen combined

	SUSPECTS		POSSIBLE TUBERCULOSIS		PROBABLE TUBERCULOSIS		ARRESTED TUBERCULOSIS		DEFINITE TUBERCULOSIS		TOTAL	
	Number	Average pounds	Number	Average pounds	Number	Average pounds	Number	Average pounds	Number	Average pounds	Number	Average pounds
Overweight and normal	3	13.0	0	0	3	4.6	5	10.0	5	12.0	16	10.1
Underweight	26	11.8	21	17.0	21	21.6	5	14.4	43	21.0	116	18.0
Total and net underweight	29	10.2	21	17.0	24	18.3	10	2.2	48	17.5	132	14.6

group III), with a net loss of 14.6 pounds for the entire body of cases under consideration. If we exclude the arrested tuberculous cases it will be noted that the loss of weight gradually increases with the certainty of the diagnosis until group V is reached, when there is a slight fall. It is difficult to explain this drop in group V except on the ground that many of the cases in this group had been previously recognized and placed under treatment with a resulting gain in weight.

TEMPERATURE

In the larger proportion of cases (79.5 per cent) the temperature was found to be normal, even among those with definite disease, in which the percentage (79.1 per cent) was almost the same as the average for the entire group of men. The temperature was more frequently sub-

TABLE 4

Temperature

	SUSPECTS		POSSIBLE TUBERCULOSIS		PROBABLE TUBERCULOSIS		ARRESTED TUBERCULOSIS		DEFINITE TUBERCULOSIS		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Subnormal	4	13.7	1	4.7	4	16.6	0	0	8	16.6	17	12.8
Normal	23	79.3	18	85.7	16	66.6	10	100.0	38	79.1	105	79.5
Over 99°F	2	6.8	2	9.5	4	16.6	0	0	2	4.1	10	7.5
Total	29	99.8	21	99.9	24	99.8	10	100.0	48	99.8	132	99.8

normal (12.8 per cent) that elevated (7.5 per cent). In the present study the temperature record was made between the hours 8:30 and 11:30 A.M., sometimes being taken immediately after the man's arrival at the clinic, and at other times after a short period of rest.

While there can be no question of the value of a temperature record, which has been taken in a careful manner at regular hours on successive days, in the clinical diagnosis of tuberculosis, in a group study like the present its value would seem questionable when one considers the expenditure of time and trouble required in securing this piece of information.

PULSE RATE

The pulse rate was increased in only a little over one-fourth (27.2 per cent) of the cases studied, which cannot be considered as a strikingly high

proportion. The presence of an increased pulse rate, however, has so much significance in regard to conditions other than tuberculosis that it seems inadvisable to omit making a record of it in any carefully made health survey.

TABLE

Pulse rate

	SUSPECTS		POSSIBLE TUBERCULOSIS		PROBABLE TUBERCULOSIS		ARRESTED TUBERCULOSIS		DEFINITE TUPERCULOSIS		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Normal	19	65.5	16	76.1	17	70.8	9	90.0	35	72.9	96	72.7
85 and over	10	34.4	5	23.8	7	29.1	1	10.0	13	27.0	36	27.2
Total	29	99.9	21	99.9	24	99.9	10	100.0	48	99.9	132	99.9

BLOOD PRESSURE

Numerous writers have called attention to the frequency with which a low systolic blood pressure is met with in cases of active pulmonary tuberculosis. We have considered it worth while reporting in detail our findings in regard to this factor.

A stystolic blood pressure of less than 120 mm. (Nicholson sphygmomanometer, reading taken by auscultation method with patient seated and arm resting on table) was found to be present in about one-third of the cases studied, or 32.4 per cent, varying between 10.0 and 45.8 per cent in the different groups. It also appeared to bear a fairly constant relation to the degree of certainty of the diagnosis. If one excludes the cases of arrested tuberculosis (group IV), it will be seen in table 6 that the percentage is lowest (13. 7 per cent) in group I (suspects), shows a decided increase (38.1 per cent) in group II (possible tuberculosis), is highest (43.8 per cent) in group III (probably tuberculosis), and for some unaccountable reason presents a slight decline (39.6 per cent) in group V (definite tuberculosis). It will be noted, however, that in this last group (V) there is the largest percentage of very low blood pressures (95 to 105). The cases of arrested tuberculosis (group IV) showed the lowest proportion of cases with a low systolic pressure, suggesting that recovery from disease is accompanied by an elevation of blood pressure.

An analysis of the 43 cases with a systolic pressure below 120 shows that the lowest percentage was among the arrested tuberculosis group

(group IV), but with this group omitted the percentage shows a gradual increase, according to the certainty of the diagnosis, the largest proportion of them (44.2 per cent) being found among the cases of definite tuberculosis (group V).

This study of the actual systolic pressure is not a very accurate method to follow, as the ages of the men varied to a considerable degree. We have, therefore, prepared the following table (table 8) showing the pro-

TABLE 6

Systolic blood pressure expressed in mm. mercury

	SUSPECTS		POSSIBLE TUBERCULOSIS		PROBABLE TUBERCULOSIS		ARRESTED TUBERCULOSIS		DEFINITE TUBERCULOSIS		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
95–105	1	3.4	0	0	2	8.3	0	0	5	10.4	8	6.0
110–115	3	10.3	8	38.1	9	37.5	1	10.0	14	29.2	35	26.4
120–125	12	41.3	7	33.3	3	12.5	3	30.0	14	29.2	39	29.5
130–135	5	17.2	3	14.3	7	29.1	4	40.0	9	18.7	28	21.2
140–145	4	13.8	2	9.5	1	4.1	1	10.0	5	10.4	13	9.8
150 and over	4	13.8	1	4.7	2	8.3	1	10.0	1	2.0	9	6.8
Total	29	99.8	21	99.9	24	99.8	10	100.0	48	99.9	132	99.7

TABLE 7

Systolic pressure below 120

	SUSPECTS		POSSIBLE TUBERCULOSIS		PROBABLE TUBERCULOSIS		ARRESTED TUBERCULOSIS		DEFINITE TUBERCULOSIS		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Systolic pressure below 120	4	9.3	8	18.6	11	25.5	1	2.3	19	44.2	43	99.9

portion of men in each group with a normal pressure, and with a pressure above or below normal taking into account the age of each person (according to Woolley's scale).

This table shows that nearly one-half of the cases (47.7 per cent) were found to have a blood pressure below normal for their age, the proportion in the various groups, with the exception of group IV (arrested tuberculosis), bearing a constant relation to the degree of certainty of the diagnosis. This sign was found present in only 27.6 per cent of the suspects

(group I), and shows a gradual increase in each group, with the exception of group IV (arrested tuberculosis), until we find 60.4 per cent of those with definite tuberculosis (group V) showing the presence of a systolic pressure below normal.

It would appear as though a low systolic blood pressure, of otherwise unexplained origin, should be considered as suggestive of the presence of tuberculosis and all cases presenting this symptom should be the subjects of more thorough and searching examinations than the average case receives. It seems hardly necessary to state that the information derived from a study of the blood pressure is of so much value from so many standpoints that no health survey could be considered complete which did not include a study of this factor.

TABLE 8

Systolic blood pressure according to normal for age

	SUSPECTS		POSSIBLE TUBERCULOSIS		PROBABLE TUBERCULOSIS		ARRESTED TUBERCULOSIS		DEFINITE TUBERCULOSIS		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Below normal	8	27.6	9	42.8	13	54.1	4	40.0	48	60.4	63	47.7
Normal	9	31.0	6	28.5	3	12.5	1	10.0	8	16.6	27	20.4
Above normal	12	41.3	6	28.5	8	33.3	5	50.0	11	22.9	42	31.8
Total	29	99.9	21	99.8	24	99.9	10	100.0	48	99.9	132	99.9

PHYSICAL SIGNS

The purpose of this paper does not include a detailed study of the physical signs which should be considered as indicative of pulmonary tuberculosis. We have, however, prepared a table (table 9) which shows the relative frequency of various groups of physical signs in the different types of cases and may be accepted as suggesting their relative frequency. It is unfortunate that we found it impracticable to show the relative frequency with which the various combinations of physical signs were encountered, but a table of this nature proved too cumbersome for practical purposes.

The most frequent signs in all the groups were apical impairment and abnormal breath sounds, as one would most naturally expect. Depression above one or both clavicles was also a very frequent finding, being present in 59.8 per cent of all the cases studied; and localized re-

traction, depression or diminished expansion occurred in nearly one-half of the cases (45.4 per cent).

Apical râles after cough (combining "after cough only" and "both before and after cough") occurred with increasing frequency with the certainty of the diagnosis, if the arrested cases (group IV) are omitted, the percentages being group I, 17.2 per cent, group II, 19.0 per cent, group III, 33.3 per cent, group IV, 0.0 per cent and group V, 39.5 per

TABLE 9

Physical signs relative frequency

	SUSPECTS		POSSIBLE TUBERCULOSIS		PROBABLE TUBERCULOSIS		ARRESTED TUBERCULOSIS		DEFINITE TUBERCULOSIS		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Depression above one or both clavicles	12	41.2	14	66.6	18	75.0	4	40.0	31	64.5	79	59.8
Localized retraction, depression or diminished expansion	7	24.1	9	42.8	10	41.6	7	70.0	27	56.2	60	45.4
Abnormal chest formation	10	34.4	10	47.6	18	75.0	3	30.0	31	64.5	72	54.5
Chest long and narrow	11	37.9	10	47.6	17	70.8	2	20.0	31	64.5	71	53.7
Poor chest expansion	5	17.2	4	19.0	13	54.1	2	20.0	24	50.0	48	36.3
Abnormal signs by percussion	28	96.5	21	100.0	24	100.0	9	90.0	47	97.9	129	97.7
Abnormal breath sounds	26	89.6	20	95.2	21	87.5	10	100.0	47	97.9	124	93.9
Apical râles, before cough only	3	10.3	1	4.7	3	12.5	1	10.0	7	14.5	15	11.3
Apical râles, after cough only	4	13.7	2	9.5	6	25.0	0	0	11	22.9	23	17.4
Apical râles, both before and after cough	1	3.4	2	9.5	2	8.3	0	0	8	16.6	13	9.8
Number of cases	29		21		24		10		48		132	

cent. The question might be raised as to why cases with apical râles after cough should be included among the suspects or possible tuberculosis cases. This is explained by the fact that while this finding was recorded at the original routine examination the sign could not be elicited on reëxamination by the physician in charge.

Sputum and X-ray examinations were not employed routinely, but in 8 of the 48 cases the sputum showed the presence of tubercle bacilli and in 14 instances the diagnosis was confirmed by X-ray examination.

GROUP V: DEFINITE TUBERCULOSIS

In order to furnish some idea of the type of cases included in group V (definite tuberculosis) we have prepared the following tables showing in a general way the extent of involvement and degree of activity in the 48 cases.

It will be seen that in 22 cases (45.8 per cent) the disease was definitely active; in a small percentage (4.1 per cent) the presence of activity was questionable; and in the remainder it was either quiescent, fibroid or possibly arrested. The involvement was slight in 19 cases (39.6 per cent) and of only moderate extent in 14 cases (29.1 per cent), while the involvement was extensive in 13 cases (27.07 per cent).

TABLE 10

Definite tuberculosis (Group V). Degree of activity

	NUMBER	PER CENT
Active	13	27.1
Moderately active	9	18.7
Quiescent	13	27.1
Fibroid	9	18.7
Possibly arrested	2	4.1
Questionable	2	4.1
Total	48	99.8

TABLE 11

Definite tuberculosis (Group V). Extent of involvement

	NUMBER	PER CENT
Peribronchial	2	4.1
Slight	19	39.6
Moderate	14	29.1
Extensive	5	10.4
Extensive (cavity)	8	16.6
Extensive (cavity)	48	99.8

FREQUENCY OF TUBERCULOSIS AND VALUE OF THE EXAMINATION

The object of the present study being to obtain information in regard to the frequency with which tuberculosis may be discovered in large bodies of men, and to see whether a survey of this kind would reveal the presence of the disease in individuals in whom its presence was unsuspected, we decided to include our findings in regard to these two points although they bear no definite relation to the subject of this article.

Table 12 shows the proportion of cases in which the presence of disease had been previously suspected and the percentage of cases revealed only by the health survey. It must be borne in mind that the examination was conducted upon two bodies of men who had to pass a physical examination before being accepted for service, and who are under the partial supervision of a surgeon who sees all cases who report for relief from duty on account of illness. For this reason one would expect to

find a lower percentage of cases of tuberculosis and fewer unsuspected cases, than one would find, for example, among a large industrial body of men who had not received the same amount of supervision.

Among the 5706 police examined we found 132 cases of pulmonary tuberculosis, an incidence of 2.31 per cent. If one considers only those cases in which the diagnosis was absolute we find 10 cases of arrested tuberculosis, an incidence of 0.17 per cent, and 48 cases of definite tuberculosis, an incidence of 0.84 per cent, a combination of the two groups showing an incidence of 1.01 per cent. If the 24 cases of probable tuberculosis are included the rate would be 1.43 per cent.

Among the 132 cases it was found that 93, or 70.4 per cent, were discovered by the health survey of the men and would probably not have

TABLE 12

Proportion of cases of tuberculosis discovered by health examination

	SUSPECTS		POSSIBLE TUBERCULOSIS		PROBABLE TUBERCULOSIS		ARRESTED TUBERCULOSIS		DEFINITE TUBERCULOSIS		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Previously suspected.....	2	6.8	4	19.0	5	20.8	7	70.0	21	43.7	39	29.5
Discovered by examination .	27	93.1	17	80.9	19	79.1	3	30.0	27	56.2	93	70.4
Total.....	29	99.9	21	99.9	24	99.9	10	100.0	48	99.9	132	99.9

been recognized until the disease had become definitely active or possibly well advanced. This statement is confirmed by the very small proportion of cases previously suspected in every group except the arrested tuberculosis and definite tuberculosis. We feel that the large number of unsuspected cases of tuberculosis revealed by the examination upon which this paper is based constitutes one of the strongest arguments in favor of this method of study of large bodies of men engaged in industrial work.

SUMMARY

1. We believe that for the early detection of pulmonary tuberculosis there can be no question that the carefully conducted health survey is the most valuable method at our command, especially valuable being the entrance examination combined with periodic reëxaminations of the entire force.

2. The diagnostic standards adopted by the National Tuberculosis Association do not appear to be applicable to those encountered in the routine examination of large industrial groups.

3. The tuberculosis incidence rates which appear in literature as the findings of medical examiners in their studies of numerous industrial bodies are so lacking in unformity and are so frequently unaccompanied by qualifying, defining, or explanatory information that they are almost valueless for comparing the findings of one industry with those of another. It would seem as though some standardized method for reporting such cases was definitely needed, before it would be possible to establish average tuberculosis morbidity rates for various occupations.

CONCLUSIONS

1. The examination of large bodies of men for the presence of pulmonary tuberculosis presents many, but not insuperable, difficulties, and in each case the diagnosis must rest upon a careful correlation of all the findings. While the most important information is that obtained by a physical examination of the patient, including inspection, palpation percussion and auscultation, there are other methods of study which possess considerable value in the formation of the diagnosis.

2. The *history* of the case is of the utmost importance but is seldom obtainable or reliable in the study of large groups of men.

3. In the routine examination of large bodies of men the recording of *temperature* seems to be of questionable value, although it may prove invaluable in the study of individual cases.

4. From the standpoint of tuberculosis the recording of the *pulse rate* offers very little if any information of value.

5. *Loss of weight* is a finding of considerable value and one which is readily obtained. The age and height must be taken into consideration in studying the weight of the individual.

6. A systolic *blood pressure* which is below the normal for the age of the patient is a very suggestive finding. The recording of the blood pressure should be included in the study of every large body of men for many reasons.

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THE OCCURRENCE OF PHYSICAL SIGNS SUGGESTIVE OF AORTIC DEFECTS.[1]

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(From the Henry Phipps Institute of the University of Pennsylvania.)

A health survey of the police and firemen of the city of Philadelphia was recently conducted by the Henry Phipps Institute of the University of Pennsylvania, having for its objects (1) the determination of the incidence of physical defects which might reduce the efficiency of or seriously interfere with the working capacity of the individual; (2) the obtaining of information upon the value of a general health survey in the detection of disease; and (3) the securing of data in regard to the best method for conducting such an examination, the time required, cost, etc. The information was desired as the Institute was planning the establishment of a department to provide general health examinations for industrial plants in and about the city of Philadelphia.

Every member of the police and fire departments was given a complete general physical examination, including a study of the height, weight, temperature, pulse, eyes, ears, nose, throat, teeth, skin, genitalia, inguinal rings, deformities and defects, blood-pressure, heart, lungs, etc. The routine examinations were performed by Drs. John S. Scouller, H. F. Keating and William R. Gilmour under the direction of the writer of this article acting as physician-in-charge. During the examination all men who were found to be normal or whose defects were only slight were dismissed, but all those in which serious defects were detected or suspected were referred to the physician-in-charge for reëxamination, who arranged for special examinations, such as Wassermann tests, roentgen-ray examinations, electrocardiographic studies, etc., either directly or in coöperation with Dr. Hubley R. Owen, chief surgeon of the police and fire departments. The blood-pressure was taken routinely in every individual and the urine examined in every case in which the systolic pressure was 150 mm. of mercury or over, or in which the examination of the urine was indicated.

[1] Read before the Thirty-eighth Annual Meeting of the American Climatological and Clinical Association, Lenox, Mass., June, 1921.

After only a small proportion of the 5706 men had passed through our hands it was found that there was a relatively large number in which the diagnostic interest was mainly centered in the aortic region. An effort was made to study these cases in detail, as far as our facilities permitted, the results forming the basis of the present paper. Special attention was given this group for the reason that it is composed of men which impressed one as being "poor risks," especially when occurring in the firemen, whose work is distinctly more strenuous than that of the policemen.

The cases under consideration were encountered under conditions which did not permit of clinical study over a long period of time, and in no case was the history of previous disease or symptomatology obtained, the cases being considered entirely on the basis of physical evidence of disease. It is, therefore, evident that we must confine ourselves to a consideration of what physical signs may be considered as definitely indicating the presumptive presence of dilatation of the aorta and what correlated evidence should be sought in an effort to discover the etiologic factor in the individual case.

Physical Signs. A description of the physical signs upon which a positive diagnosis of aortic disease may be based is an exceedingly difficult one, as the writers upon this subject are not in complete accord and frequently are not as clear as one would desire. This is due to the fact that their descriptions are usually confined to special diseases while the physical signs vary with the pathologic changes in the aorta.

It is not my purpose or desire to enter into a discussion of the various manifestations of arterial disease but to confine myself to a consideration of the abnormal physical signs which may be encountered in the routine examination of a large number of men, signs which suggest pathologic changes in the aorta.

The signs which have been attributed to elongation, dilatation, sclerosis or inflammation of the aorta are briefly as follows: Dulness over the manubrium, extending to the right in the 2d and 3d interspace, with or without localized pulsation recognizable by inspection or palpation.

Accentuation of the aortic second sound which may often be clanging in character or possess a tympanic quality and may frequently be accompanied by a palpable diastolic shock.

A systolic murmur may be present at the aortic cartilage which occasionally may be transmitted to the vessels of the neck and may at times be accompanied by a systolic thrill.

Others signs which have been noted are: Visible pulsation in the peripheral arteries, displacement of the right subclavian upward to a position above the clavicle, suprasternal pulsation, abnormal mobility of the apex-beat with change of position, pericardial friction rub and other signs associated with mediastinal inflammation or peri-aortitis.

The signs which have been considered of most value are manu-

brial dulness and alteration in tone of the second aortic sound, the latter being considered of the greatest value in recognizing aortitis in its earlier stages.

During our examination of the police and firemen we encountered 49 cases which presented evidence suggesting the presence of aortic changes. One of these, a man aged thirty-six years, with a definite specific history, showed signs definitely pointing to the presence of an aneurysm, the diagnosis being confirmed by roentgen-ray examination. This we have omitted from our series, leaving 48 cases for consideration. It will be noted that in many of the cases the records are incomplete, certain of the physical signs having apparently been omitted or not recorded. This is due to the fact that at certain periods during the examination time did not permit of as thorough an examination as one would desire or else in the rush of work the findings were not completely recorded. Failure to report for special laboratory studies, such as Wassermann tests, roentgen-ray and urine examinations, largely accounts for the omissions in laboratory reports.

While these omissions may detract from the scientific value of the observations in this study, they in no way affect the primary object of this paper, which is to call attention to the relative frequency (at least in the group studied) with which physical signs may be encountered strongly suggestive of pathologic changes in the aorta. A very important feature was the almost total absence of any suspicion on the part of the individual that he was not in good health.

For convenience in presenting the cases we have arranged them in groups according to the skiagraphic findings as follows:

		Cases
Group I.	Roentgen-ray shows definite aortic changes	9
Group II*a*.	Roentgen-ray shows slight aortic changes	8
Group II*b*.	Roentgen-ray shows questionable aortic changes . . .	3
Group III.	Roentgen-ray shows absence of aortic changes	13
Group IV.	No roentgen-ray examination made	15

The roentgen-ray studies were made by Dr. Alfred S. Doyle, assistant to Dr. H. K. Pancoast, roentgenologist to the University Hospital.

Tables have been prepared showing each case studied, the more important physical signs observed and such correlated clinical data as might be of interest.

The first 7 men in this group, all over forty-seven years of age, showed a definite dilatation of the aorta. A study of the physical signs recorded in these cases would indicate that the character of the second aortic sound, with a systolic aortic murmur or manubrial dulness, was the most characteristic sign of the dilatation. The 2 cases without accentuation of the aortic second were ones in which the blood-pressure was normal. (See Table I.)

GROUP I.—DILATATION OF AORTA WITH X-RAY EXAMINATION.

Case No.	Age.	Accentuated aortic second sound.	Aortic systolic murmur.	Dulness over manubrium.	Wassermann test.			Urine examination.					Blood-pressure.			Associated cardiac defects, physical signs and symptoms.	Report of Roentgen-ray examination of aorta and lungs.
					Positive.	Negative.	Omitted.	Normal.	Specific gravity.	Albumin.	Sugar.	Omitted.	Systolic.	Diastolic.	Pulse pressure.		
1884	52	++	+	−	..	..	+	..	1006	Tr.	0	..	170	90	80	Aortic regurg.?	First portion of arch broad and pulsating; mod. dilatation of entire arch, especially the ascending portion.
3945[1]	53	+	+	−	..	..	+	..	1012	Pres.	0	..	205	140	65	Extrasystoles	Decided widening of aorta; no unusual pulsation.
3207	48	+	+	−	+	..	..	+	−	..	..	..	140	80	60	Mitral insuf.	Widening of arch and marked pulsation.
3939	60	+	+	−	..	+	..	..	1012	Tr.	+	..	185	110	75	Mitral insuf.?	Marked dilatation of arch and considerable pulsation; almost aneurysmal.
2133	50	+	0	+	..	+	..	..	1024	Ft. tr.	0	..	205	125	80	Pain over sternum	Considerable enlargement of transverse and descending portions of arch.
3725	50	0	+	−	..	+	..	+	−	..	..	..	125	70	55	Mitral insuf.? and aortic regurg.?	Increase in size of first portion of arch and fairly marked expansile pulsation; slight dilatation ascending arch (old tb.?).
3823	68	0	+	−	..	..	+	..	..	..	..	+	130	80	50	Aortic regurg. and rel. mitral insuf.?	Widening of first portion of arch in both directions (old pulm. tuberc.?).
5085	41	0	+	−	..	..	+	+	1021	..	..	..	155	80	75	Aortic regurg.	Arch not dilated but marked expansile pulsation (pulm. fibrosis).
2895	41	0	0	−	..	..	+	..	..	..	..	+	120	80	40	Pulsation below left clavicle, out to mid-clavic. line	Tortuous aortic arch, especially in second left interspace.

[1] Died suddenly since examination.
[2] Has resigned (on account of ill health?) since examination.

Case No.	Age.	Accentuated aortic second sound.	Aortic systolic murmur.	Dulness over manubrium.	Wassermann test.			Urine examination.					Blood-pressure.			Associated cardiac defects, physical signs and symptoms.	Report of Roentgen-ray examination of aorta and lungs.
					Positive.	Negative.	Omitted.	Normal.	Specific gravity.	Albumin.	Sugar.	Omitted.	Systolic.	Diastolic.	Pulse pressure.		
58	41	+	+	−	..	+	..	..	..	..	..	+	145	90	55	Prominent superficial veins over chest	First portion of arch a little widened in both directions.
3922	57	+	+	−	..	+	..	..	1006	Ft. tr.	0	..	140	80	60	Extrasystoles; auric. fibrill.?	Slight dilatation of ascending arch.
22	35	++	0	+	..	+	..	..	..	..	..	+	130	95	35	....	Slight dilatation of ascending arch.
5325	57	+	0	+	..	..	+	..	1020	Ft. tr.	0	..	180	110	70	Cardiac dilatation	Ascending arch slightly widened in oblique position.
3893	66	0	+	−	..	+	..	..	−	Cl.	0	..	155	95	60	Rel. mitr. insuf.; auric. fibrill. (electrocard.)	First portion of arch slightly increased in width.
2157	51	0	+	−	..	+	..	+	−	..	..	..	155	90	65	Aortic and mitral regurg.	Aorta slightly tortuous and slightly dilated in ascending portion; no aneurysm.
3744	54	0	+	−	..	+	..	+	1010	..	..	..	125	85	40	Rel. mitral insuf.	Slight increase in width of first portion of arch in both directions; pulsation not marked.
2068	40	0	0	−	..	..	+	..	..	..	..	+	145	80	65	Mitral regurg.?; heart irreg.; visible pulsation in vessels.	Arch of aorta slightly increased in width.

GROUP II B.—QUESTIONABLE DILATATION OF AORTA WITH X-RAY EXAMINATION.

Case No.	Age	Accentuated aortic second sound.	Aortic systolic murmur.	Dulness over manubrium.	Wassermann test.			Urine examination.					Blood-pressure.			Associated cardiac defects, physical signs and symptoms.	Report of Roentgen-ray examination of aorta and lungs.
					Positive.	Negative.	Omitted.	Normal.	Specific gravity.	Albumin.	Sugar.	Omitted.	Systolic.	Diastolic.	Pulse pressure.		
3281	53	+	+	−	..	+	..	..	1036	Tr.	+	..	195	95	100	Mitral insuf.	Arch possibly slightly increased in oblique view.
2890	53	0	+	−	..	+	..	+	−	..	..	..	125	80	45	Mitral regurg.?	Slight widening of ascending arch in ant.-post. and oblique views, but not unusual for age.
2264	44	+	+	+	..	+	.	.	..	..	.	+	135	80	55	.....	Good pulsation of ascending arch which is possibly slightly broadened but not to an unusual degree.

GROUP III.—AORTIC CHANGES SUSPECTED CLINICALLY, WITH NEGATIVE X-RAY FINDINGS.

Case No.	Age.	Accentuated aortic second sound.	Aortic systolic murmur.	Dulness over manubrium.	Wassermann test.			Urine examination.					Blood-pressure.			Associated cardiac defects, physical signs and symptoms.	Report of Roentgen-ray examination of aorta and lungs.
					Positive.	Negative.	Omitted.	Normal.	Specific gravity.	Albumin.	Sugar.	Omitted.	Systolic.	Diastolic.	Pulse pressure.		
365	42	+	+	+	..	+	..	+	1005	..	..	..	155	75	80	Rel. mitral insuf.	Negative.
439	35	+	+	+	..	+	..	..	..	..	..	+	155	90	65	Rel. mitral insuf.	Negative.
724	53	+	+	+	..	+	..	..	..	..	..	+	170	85	85	.....	Negative.
2820	36	+	+	+	..	+	..	..	..	..	..	+	125	75	50	Mitral regurg.	Negative.
4627	62	+	+	+	..	+	..	..	1020	Tr.	0	..	160	70	90	Aortic regurg.	Aorta not enlarged to any unusual extent.
189	43	0	0	+	..	+	..	..	..	..	..	+	130	85	45	.....	Negative.
485	29	0	0	+	+	..	..	+	1015	..	..	..	185	100	85	.....	Negative.
1806	37	0	+	+	..	+	..	..	..	..	..	+	125	85	40	.....	Negative.
4530	22	0	+	+	..	+	..	..	1007	V. ft. tr.	0	..	165	85	80	Soft double aortic and systolic murmur at apex; reëxam. neg.	Negative.
5397	46	0	+	0	..	..	+	..	..	..	..	+	130	80	50	.....	Negative.
2272	52	0	+	+	..	..	..	+	1025	..	..	..	155	95	60	.....	Negative.
2900	65	0	+	+	..	+	..	..	1022	V. ft. tr.	+	..	155	100	55	Rel. mitral insuf.; chronic myocarditis	Negative.
1934	52	0	0	+	+	..	..	..	1017	V. ft. tr.	0	..	140	85	55	.....	Negative.

GROUP IV.—AORTIC CHANGES SUSPECTED CLINICALLY, NO X-RAY EXAMINATION MADE.

Case No.	Age.	Accentuated aortic second sound	Aortic systolic murmur.	Dulness over manubrium.	Wassermann test.			Urine examination.					Blood-pressure.			Associated cardiac and pulmonary defects and physical signs.
					Positive.	Negative.	Omitted.	Normal.	Specific gravity.	Albumin.	Sugar.	Omitted.	Systolic.	Diastolic.	Pulse pressure.	
4649	63	++	0	++	..	..	+	+	1023	..	..	..	165	105	60	Myocarditis; auric. fibrill.?
1112	64	++	+	+	..	..	+	+	1010	..	..	..	185	30	155	Rel. mitral insuf.?
4526	26	+	+	+	+	..	..	..	1021	Cl.	0	..	175	85	90	Mitral regurg.?
5549	50	+	+	+	..	..	+	..	1020	V. ft. tr.	0	..	190	120	70	Mitral regurg.
471	29	+	0	+	..	+	..	+	1002	..	..	..	180	90	90	
1801[1]	52	+	0	+	..	..	+	..	..	..	..	+	155	85	70	
4551	37	+	0	+	..	..	+	..	1020	V. ft. tr	0	..	160	100	60	Cardiac hypertrophy; overacting heart.
4393	38	0	+	+	..	..	+	..	1007	V. ft. tr.	0	..	155	75	80	Visible pulsation in vessels.
4328	41	0	+	+	..	..	+	..	..	..	..	+	115	80	35	Mitral regurg.?
5103	50	0	+	+	..	..	+	..	1027	Cl.	0	..	165	105	60	Extrasystoles; aortic regurg.
841	49	0	+	+	..	..	+	..	..	..	..	+	140	65	75	Mitral sten. and regurg.; mitral regurg.
2939	60	0	+	+	..	..	+	+	1016	..	..	..	165	90	75	Emphysema.
2356	59	0	+	+	..	..	+	..	..	..	..	+	130	75	55	Mitral regurg.
3236	60	0	+	+	..	+	..	..	1020	V. ft. tr.	0	..	150	80	70	Mitral regurg.; aortic and mitral regurg.; auric. fibrill.?
3435	44	0	+	+	..	..	+	..	..	..	..	+	130	50	80	Marked suprasternal pulsation.

[1] Died since examination (of uremia?).

It must be borne in mind that the record of "accentuation of the second aortic sound" refers merely to accentuation and not to the quality of the second sound itself. These 48 cases were considered as possible cases of aortic disease on account of the fact that they presented signs which we considered indicative of aortic disease, the sign which we laid most stress upon being the clanging quality of the aortic second sound. The record of "accentuation of the aortic second sound" must not be taken to represent this change in the quality of the sound.

Of the two remaining cases one showed no dilatation but marked expansible pulsation by the fluoroscopic examination, with a systolic aortic murmur in a case of aortic regurgitation, and one showed an abnormal pulsation below the left clavicle due to a tortuous aortic arch, especially marked at this point.

This group consisted of 8 cases in which the roentgen-ray revealed slight increase in width of a portion of the aorta, and yet the various physical signs occurred with about the same relative frequency as in Group I. It will be noted that in this group the systolic blood-pressure was, as a rule, lower than in Group I, an average of 147 compared to 159. (See Table II*a*.)

Here the signs also occurred with fair constancy even in three cases with questionable roentgen-ray findings. (See Table II*b*.)

This group consists of 13 men in which the roentgen-ray examination was negative, but in all of which definite physical signs were noted pointing to aortic changes. In two cases (485 and 1934) a positive Wassermann test was obtained and may be considered as cases of specific aortitis without dilatation or marked elongation of the aortic arch.

In 5 cases the Wassermann test was not made so that they may be considered as possible cases of aortitis. There were, however, 6 cases in which the Wassermann test was negative and which showed definite physical signs of aortic change with negative roentgen-ray findings. In these cases it is difficult to explain the apparent discrepancy between the physical findings and the roentgen-ray study. In 1 case there was a slight albuminuria with hypertension in a young man aged twenty-two; in 2 other cases the systolic blood-pressure was rather high for the age and in 2 the pressure was normal. (See Table III.)

There were 15 cases in which no roentgen-ray examination was made and with 3 exceptions no Wassermann test. These were nearly all cases presenting evidence of cardiac disease in addition to the suspected aortic change, many of them also showing albuminuria. (See Table IV.)

Summary. In the examination of large bodies of men more attention should be directed to the study of the upper anterior chest than is usually devoted to this region, especially, but by no means exclusively, in those over forty years of age. In the present

study of 5706 men with an average age of forty-five to forty-nine years, signs were found suggesting changes in the aorta in about 0.85 per cent. The literature on this subject is surprisingly scanty when one considers the importance of the condition. The statement has been made by Clifford Allbutt[2] that "Chronic disease of the ascending aorta without aneurysm is far more common in middle life, in early adult life and even in youthful life than we are wont to realize, and is for the most part insidious." An observation which the present study would appear to confirm.

The nature of our study was of such a character that it is impossible to arrive at any very definite conclusions as regards to etiology; 5 showed a positive Wassermann reaction (including the case of aneurism), in 20 it was negative and in the remaining 24 it was not taken. In only 3 instances was sclerosis of the peripheral arteries (radials) noted among the 44 cases in which a positive Wassermann test was not present or not made, although the absence of sclerosis in the peripheral vessels does not exclude the possibility of aortic change. In an effort to show the type of case in which this condition was noted we have prepared the following table:

TABLE SHOWING ASSOCIATED DEFECTS (CASES WITH POSITIVE WASSERMANN TESTS BEING ELIMINATED.)

	Wassermann test negative.		Wassermann test not made.		Total.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
Hypertension:						
Cardiorenal	7	35.0	2	8.3	9	20.4
Cardiac	3	15.0	4	16.6	7	15.9
Renal	1	5.0	6	25.0	7	15.9
Alone	1	5.0	2	8.3	3	6.8
Slight—urine not examined	0	0	2	8.3	2	4.5
Cardiac	0	0	5	20.8	5	11.3
Questionable	3	15.0	1	4.1	4	9.0
None—urine not examined	5	25.0	2	8.3	7	15.9
Total	20	100.0	24	99.7	44	99.7

It will be noted that the large proportion of cases were associated with some degree of hypertension, in 60 per cent of those with negative Wassermann test and in 64.5 per cent of those in which no Wassermann test was made. This corresponds with the observations of Smith and Kilgore,[3] who found frequent dilatation of

[2] Diseases of the Arteries, including Angina Pectoris, 1915, **2**, 190.
[3] Am. Jour. Med. Sc., April, 1915.

the arch in their roentgen-ray study in individuals under the age of fifty years in non-syphilitic conditions, especially in chronic nephritis with hypertension.

In conclusion, we would state that in the examination of a large number of men, non-syphilitic cases are encountered with relative frequency in which the physical signs strongly suggest the presence of aortic changes, which may or may not be appreciable by roentgen-ray examination.

TUBERCULOSIS AS IT AFFECTS THE INDUSTRIAL WORKER

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TUBERCULOSIS AS IT AFFECTS THE INDUSTRIAL WORKER*

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THE relationship between tuberculosis and the industrial worker is so complicated and involved, and presents so many phases of interest to the industrial physician, that it would be impossible to do more than refer briefly to certain of the more important phases of the subject. There is no disease which is so important from the standpoint of the industrial physician, as it appears in so many varied forms and may so completely disable the workman, frequently after a prolonged period of partial disability with the loss of a considerable amount of time and efficiency. The onset is usually so insidious that the disease becomes well advanced before its true nature is recognized.

During recent years great stress has been laid upon the importance of childhood infection with tuberculosis, and the frequency of adult infection has been questioned, but the studies upon which this view is based are of such a character that it would seem inadvisable to neglect any of the precautions which have hitherto been employed to prevent the dissemination of the tubercle bacilli among adults. In industry the detection of the disease is of the utmost importance to the employer, the employee affected, and his fellow-workers.

The relationship between tuberculosis and industry constitutes one of the most important problems bearing upon the prevention of this disease, the solution of which unfortunately presents many difficulties. It is almost impossible to determine in any individual case how important a part has been played by occupation, and to what extent home environment and mode of living have been responsible for the development of the disease. A weak point in most of the studies of tuberculosis in industrial bodies lies in the fact that the home conditions of the workers have been ignored. The disease is extremely prevalent among the poor industrial workers—that large group which is usually exposed to crowded, poor living conditions, poor food, dissipation, and similar factors which we know may be responsible for the development of the disease and may favor its spread.

There can be no question that working under unfavorable conditions results in an increase of the disease and that improvement of the general hygienic conditions of the plant is followed by a reduction in its frequency. Industry, then, bears the same relation to tuberculosis that the home environment bears to it; it is just as essential that the working conditions should be favorable as that the home conditions should be. In studying tuberculosis in any given industry, one must not only consider the special trade processes involved, but also the general conditions as to light, ventilation, etc. There are certain trade processes and occupations, especially those in which irritative types of inorganic dust constitute a hazard, which have such a high mortality rate from

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tuberculosis that they have always been regarded as definite predisposing factors.

The effects of industry have been summarized by Dr. Hayhurst (1) as follows: (1) deaths from industrial diseases are rare; (2) specific occupational diseases, such as, for instance, those due to poisons, are fairly common; (3) nonspecific occupational diseases, represented by chronic infections and degenerative processes, are very common; while (4) health complaints in which the occupation enters as a chief factor are almost universal. He further states, "It is startling when we realize that such an innocent occupation as that of the telephone girl is associated with a tuberculosis rate of 43 per cent. of all deaths among this class of workers, and that the stenographer suffers a rate of 39 per cent. from the same disease."

Another phase of the tuberculosis problem of considerable practical importance, especially from the standpoint of the industrial plant, is the relationship between pulmonary tuberculosis and trauma. Evidence regarding a sufficient number of cases has been established in which tuberculosis has followed traumatism—in individuals known to have been free of all evidence of the disease prior to the injury—to warrant one in accepting trauma as a possible cause for the development of the disease. The physical examination of applicants for employment and the frequent re-examination of employees are the only means of protection which a plant possesses against being unjustly held responsible for tuberculosis in persons who, when injured, claim that the traumatism is responsible for the disease.

When one studies the frequency with which tuberculosis is encountered in industrial bodies, one encounters difficulty in securing data so formulated that a definite comparison of one plant with another can be made. Some statistics refer to males, some to females, and others to both sexes. In some instances where both sexes are included, the proportion of males and females, with the corresponding rates, is not given. Often no mention whatever is made of the sex of the workers. Similarly, no distinction is made between white and colored workers. Very few statistics give the average age of the workers and practically none are arranged according to age group. Rarely is mention made of the exact occupation of the individuals affected. Occasionally the number of examinations is given, but generally no reference is made to the total number of workers employed, the reason for the examination, the method of examination, or the grounds upon which the diagnosis was based, etc. Some physicians employ the term "serious lung defect," and fail to state the nature of the defect; some include suspected tuberculosis and definite tuberculosis under one heading; others include them under separate headings. It is not surprising, in view of this lack of uniformity, that the tuberculosis incidence rates in Table 1, which I have collected from various sources, show such an exceedingly wide variation, running all the way from 0.02 per cent. to 6 per cent. The definite tuberculosis cases in which the complete figures are given show an average of 1.494 per cent.

The great variation between the findings of the different authors in various industries cannot be accepted as being indicative of the influence of the industry itself upon the prevalence of the disease, as there are too many other factors which must also be taken into consideration—such as age, sex, color, methods employed, and the individual opinion of the examining physician as

to what physical signs and symptoms are to be considered as indicating the presence of the disease, and as to what care was exercised in making the examination. This personal equation of the examining physician is probably one of the most important factors involved. While the incidence rates given in this table are by no means constant, they are sufficient to indicate that the disease is so generally prevalent as to warrant our employing every possible means to prevent it.

Viewing the problem from a slightly different angle, it is interesting to see how many days per employee are lost annually through tuberculosis. In his excellent article on industrial absenteeism, Dr. Quinby (18) states that in the industrial plant of which he is medical director pulmonary tuberculosis was responsible for the loss of 0.246 days per employee during the year 1920. Excluding acute infections of the upper respiratory tract, tuberculosis had the second highest rate of any disease or group of diseases. Diseases of the stomach had a higher rate (0.297), and rheumatism had a slightly lower rate (0.235). This gives one a clear appreciation of the importance of tuberculosis from the industrial standpoint.

Fortunately, we have at our command a method of detecting tuberculosis among industrial workers, namely, by means of entrance examinations combined with periodic health examinations. If carefully conducted, this procedure will undoubtedly help materially to reduce the number of cases within a relatively short period of time, provided the hygienic condition of the plant is good. It must be borne in mind, however, that by examinations I mean complete examinations for all defects and diseases, for it is neither practical, economical, nor expedient to conduct an investigation of this kind for the detection of one disease alone. As a matter of fact, every defect or disease detected and corrected, and every step taken to improve the health and well-being of the individual is a step toward the prevention of tuberculosis.

The entrance examination has been fairly generally employed and is in operation in a large number of plants because it is a procedure which more readily appeals to the employer, promising a definite, tangible return by eliminating the seriously disabled and diseased workmen, and also serving as a control on the type of work which may be performed by workmen with a moderate disability, preventing them from engaging in an occupation which would aggravate their defects. The results to be obtained by periodic health examinations are not so obvious to the employer, and consequently it is difficult to convince him of the value of a health program in which both entrance examinations and periodic health examinations are included.

While the entrance examination may serve to keep out of the plant seriously diseased individuals and may help to place men at work for which they are physically fitted, it is concerned only with the new employee — usually the least valuable to the plant—and does not include the valuable workmen who have been in the employ of the plant for some time. Any attempt to keep these older employees under observation by examining them when sick is of relatively little value to the plant; they should be examined periodically before they become actually ill, when the first manifestations are present, and at a time when a change of occupation, perhaps, or treatment while at work may be sufficient to prevent illness.

Tuberculosis is a disease which, like

TABLE I.—TUBERCULOSIS RATES IN INDUSTRIAL STUDIES COLLECTED FROM VARIOUS SOURCES

Author	Industry	Title of Defect	No. of Cases	Incidence Rate %	No. Examined	Applicants	Employees	Male
(2)	electric mfg. co.	serious lung defect	17	0.09	18,390		X	X
	" " "	" " "	44	0.14	29,805		X	X
	" " "	" " "	90	0.50	17,858		X	X
	" " "	" " "	2	0.05	3,628		X	
	" " "	" " "	4	0.07	5,583		X	
	" " "	" " "	1	0.03	2,944		X	
(3)	leather works and cannery	unquestionable tuberculosis	—	0.80	1,500	X	X	X
an (4) ...	steel company	lung disease	35	0.28	12,302	X	X	X
	" "	" "	59	2.42	2,430	X	X	X
g (5)	department store	active tuberculosis	19	3.80	500			
		inactive tuberculosis	8	1.60	(2,000 employees; 85% females)		X	X
	" "	active tuberculosis	6	3.00				
		inactive tuberculosis	2	1.00	200	X		X
g (6)	" "	tuberculosis	42	3.47	1,210		X	X
(7)	grinding company	lung rejections	5	0.19	2,618	X		X
(8)	" "	pulmonary tuberculosis	10	0.50	2,000	X		X
l (9)	not stated; medium but hazardous	tuberculosis	1	0.33	300	X		X
n (10)	International Harvester Co.	"	—	0.88	about 20,000		X	X
			—	0.54	" "		X	X
schewsky (11)	garment workers	pulmonary tuberculosis	65	3.11 } 2.49	{ 2,086		X	X
	garment workers	the same	9	0.9 }	{ 1,000		X	
(12)	bakers	" "	—	2.40	800			
	tailors	" "	—	1.60	800			
	tobacco workers	" "	—	1.30	600			
	furriers	" "	—	6.00	83			
13)	insurance policy holders	possible tuberculosis of lungs	—	1.40	— -		X	X
	commercial employees	the same	—	0.90	- - -		X	X
(14)	clerks, 35% light skilled, 20% heavy mfg. and laboring, 45%	active tuberculosis	—	1.70	112,000		X	58%
	miscellaneous, reports of ten surgeons	" "	—	1.40	— —		X	
	steelworkers—U.S.P.H.S.	" "	—	0.92	936		X	
on and on (15)	miscellaneous	pulmonary tuberculosis	—	1.07 } 1.10	14,049		X	X
.....	policemen and firemen	the same	103	1.80	5,883 5,706		X X	X
epartment	drafted men	pulmonary and suspected tuberculosis	—	2.202	— —			X
	drafted men in Pennsylvania	the same	—	1.947	— —			X
17)	telegraph co.	tuberculosis	36	0.49	7,201	X		69%

many others, usually develops insidiously, the patient frequently not considering himself ill until the disease is well developed or even advanced. This fact was strikingly illustrated in the examination of the policemen and firemen of the city of Philadelphia, recently conducted by the Phipps Institute of the University of Pennsylvania, in which nearly two-thirds (64 per cent.) of the cases of tuberculosis discovered had previously been entirely unsuspected, even by the affected individuals themselves.

In order to prevent the infection of other workmen and to secure a retention of the working capacity of the individual affected with tuberculosis, with the loss of only a relatively short period of time, the disease must be discovered early. There is no method for this early detection of disease which is at all comparable with periodic health examinations.

For the foregoing reasons I would like to make a special appeal for the installation of this method of study in every industrial establishment. While serious objection will, no doubt, be raised to such an elaborate and time consuming procedure, I believe that the difficulties are not insuperable and that the results obtained would more than compensate for the cost involved. It is impossible to estimate how great would be the influence upon the public health of a widespread employment of periodic examinations. A recent study of periodic health examinations by one of the large insurance companies has clearly demonstrated their economic value to such an organization, and I can see no reason why they would not be of equal financial value to an industrial plant. There can be no question that, from the standpoint of tuberculosis at least, the general employment of periodic physical examinations would constitute one of the most effective measures that could be devised for the advancement of preventive medicine.

To be of value it is essential that the examinations be made with thoroughness, care, and precision; otherwise the early cases of tuberculosis will be overlooked. There is no disease which varies more in its clinical manifestations than does tuberculosis; in some cases the general symptoms predominate, and in others the pulmonary signs are most marked. The latter type of case is more easily recognized by the examining physician than the former, which is frequently confused with some other disease. While the early recognition of the disease is not always easy, in the majority of cases a careful examination will reveal its presence. It is a mistake to view the early diagnosis of pulmonary tuberculosis as a very difficult procedure requiring expert training, employment of the roentgen rays and similar costly methods. More early cases pass unrecognized, through carelessness or neglect to examine, than are undetected on account of lack of training. There are, to be sure, a certain number of cases which tax one's diagnostic ability very severely, but they constitute only a relatively small proportion of the total number.

The cases which present the most difficulty are those in which there are symptoms or general signs suggesting the presence of tuberculosis, but in which the physical signs in the chest are indefinite or obscure; or, on the other hand, those in which there is definite evidence of pulmonary disease, suggesting tuberculosis, in which the sputum remains negative for tubercle bacilli. In both of these types of cases it may be found necessary for the in-

dustrial physician to seek the assistance of some one who has had considerable experience in diseases of the chest and who has access to laboratory facilities which will aid him in establishing a diagnosis.

The method to be employed in carrying out entrance examinations is so well known that it is unnecessary to refer to it at this time. The periodic health examinations constitute more of a problem, the method of procedure varying with the size of the plant, the number of workmen that can be spared from work at one time, the medical equipment of the plant, etc. The frequency with which they should be carried out is also a difficult question to decide, as I have so far been unable to discover any accurate studies which would throw any light on this question. In very hazardous occupations it is customary to make examinations at frequent intervals, even every month, but in the average plant they are made at intervals of one, two or three years, according to the judgment of the medical officer.

The industrial plant with a medical staff of its own should experience no difficulty in making periodic health examinations, provided they were taken into consideration at the time when the medical staff was organized, or provided the personnel is increased to permit their being made. They may be made continuously throughout the year, each employee reporting for re-examination about one year from the time of employment and again each succeeding year, or it may be less disturbing to conduct an intensive study of all employees within a short period of time, preferably during the slack season. For the latter method it may be necessary to have the examinations conducted by some outside agency in order to avoid interfering with the routine medical service of the plant.

The plant which has no regular medical officer or only a part-time physician will find it almost impossible to have periodic health examinations made without the help of some outside agency unless the number of employees is so small that the part-time physician can make the examinations along with his routine work.

The need for some organized agency, which could assist in the work of conducting health surveys and could serve as a group diagnostic center for obscure cases, so impressed the Henry Phipps Institute that it organized such a team of examiners and established a diagnostic clinic for the use of industrial plants in and about Philadelphia, the object being to provide a service which would cover all disabilities and not merely tuberculosis. The recent period of business depression seriously interfered with the health survey work but the diagnostic clinic is now in operation and is handling cases from several large industrial establishments.

Summary

In the foregoing paper I have attempted to give an outline of the tuberculosis problem as it affects the industrial worker. An unusual opportunity is here offered for the introduction of preventive measures, such as, for example, periodic health examinations, the results of which would be felt in the industries themselves and, if sufficiently widespread, would have a beneficial effect upon the health of the public. The review of the subject has also made evident the need for a more carefully developed and more uniform method of statistical report.

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Some Industrial Phases of Tuberculosis*

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TUBERCULOSIS is undoubtedly one of the most important problems which today confront those interested in the public health and welfare. Numerous investigators have devoted a vast amount of attention to the methods to be employed in the prevention of this disease, the question being considered from almost every conceivable angle. There is no more important aspect of this entire subject than that which deals with the relationship between this disease and the industrial worker and his environment. Until a comparatively recent time the campaign of prevention was chiefly directed toward the eradication of disease from among the very poor, for it is in this group that the disease is most widespread and causes the greatest amount of suffering and loss of life.

Within recent years more attention has been paid to the study of this disease among that extremely important social group, the industrial workers, and a greater effort is being made to bring about a reduction in the incidence of the disease. While perhaps not quite so prevalent in this body as among the very poor, the industrial workers constitute such a large proportion of the population and are such an important factor in the welfare of the nation that special importance is attached to the occurrence of the disease in this group.

There are several features of the industrial aspect of this general problem which call for special consideration, because, while every measure instituted for the welfare of the public at large exerts a favorable influence upon this special group, the industrial workers are exposed to certain risks and factors which are peculiar to themselves, and which are not reached by any measures directed toward the prevention of the disease among the general public. If the tuberculosis campaign is to attain its object these special features must be taken into account, and adequate preventive measures devised and put in operation.

Before it is possible effectually to handle the industrial phase of this problem it is essential that we secure reliable information concerning the actual incidence of the disease among the workers in the different industries, and, more especially, in the different occupations involved in these industries, as nothing can be more misleading to those interested in the relation between the occupation and disease, than the employment of such vague, general terms as hatter, steel workers, etc., to designate the work performed by the individual. A thorough knowledge of the disease as it affects those engaged in definite trade processes must be obtained if it is to be attacked in an intelligent and efficient manner.

Records Are Inadequate

To secure this knowledge it is necessary that a more careful and systematic method be devised for recording the incidence of disease among the workers, and so perfected and extended that it will include not only the large plants with their well organized and effective medical depart-

*Read before the Seventh Annual Meeting of the American Association of Industrial Physicians and Surgeons, St. Louis, Mo., May 22-23, 1922.

ment, but also the smaller plants or shops with only a relatively few workers and little or no medical supervision. Until such a comprehensive system can be devised much can be done toward its development by the compiling and standardizing of the records in the industrial plants which are at present equipped with a medical service. Most of the reports published by industrial physicians at the present time are so lacking in uniformity in their methods of tabulation and their standards of defects vary so greatly that they are almost valueless for comparative statistical purposes. A recent attempt to compile the available data on the incidence of tuberculosis among industrial workers[1] was practically valueless owing to the absence in most cases of any statement of the diagnostic standards upon which the figures of the various observers were based, and the lack of specific mention of the various occupations involved, the method of examination, and such important additional data as sex, age, etc., of those examined.

1. Craig, F. A.: "Tuberculosis As It Affects the Industrial Worker." Read before the Section on Industrial Medicine and Surgery, the College of Physicians of Philadelphia, to appear in the American Review of Tuberculosis.

While accurate information in regard to the prevalence of the disease is essential for a complete and efficient campaign against this disease, there are certain measures which may in the meantime be employed with advantage by the industrial physician in his efforts to check this disease. Before considering these in more detail as they apply to the industrial problem, it may be of interest to outline briefly the plan employed at the present time in the general campaign against this disease, as it is along these same lines that the industrial program will have to be formulated.

The prevention of tuberculosis has been carried out along two main lines, which may be termed: (1) the prevention of infection; and (2) the prevention of disease. Under the first heading may be included all those measures which are concerned with the dissemination of the tubercle bacillus; such as the prevention of promiscuous expectoration, destruction of the sputum, isolation of the infective case, early recognition of the disease, and similar procedures, dependent upon the education of the public for their successful application.

The second division includes those

TABLE I.—Sanatorium of Tuberculosis Disease* Collective Data, 1909-1919 American and Canadian Experience.

Condition at discharge	Condition at entry					
	Incipient cases		Moderately advanced cases		Far advanced cases	
	No.	Per cent	No.	Per cent	No.	Per cent
Apparently arrested	5,373	34.0	1,162	4.1	134	0.5
Improved	3,983	25.1	11,308	40.2	7,146	28.0
Quiescent	4,739	30.0	9,572	34.0	2,236	8.8
Unimproved	1,623	10.3	4,958	17.6	7,563	29.7
Died	89	0.6	1,138	4.1	8,405	33.0
Total	15,807	100.0	28,138	100.0	25,484	100.0

*Based on Chart showing general results of sanatorium treatment in 69,500 cases, regardless of length of stay or method of treatment. Published by the Prudential Insurance Company of America. Journal of the Outdoor Life, January, 1922, p. 30.

means which have to do with the raising of the standard of living and health of the individual to such a point that, even in cases of infection, the disease will not develop owing to increased resistance to the tubercle bacillus. We have no means at our command to increase this resistance which can be compared to the results obtained by an improvement in the general health and well being and the maintenance of this state. The successful application of the principles involved in this second division depends upon the improvement of the general living and working conditions; good food, and all that this phrase implies; proper and sufficient recreation; the prevention of other diseases and the correction of all defects; proper medical care and attention during pregnancy, illness, and following accidents; and every similar measure which will add to the general health, strength, and well being of the individual.

The application of these general principles to the special field included under the name "industry," would suggest the formulation of the following program:

Health Talks

Health talks to the employees should include such subjects as would cover the general hygiene of the body, including cleanliness, care of the teeth, exercise, rest, food, fresh air; and the importance, means of prevention and general rules of treatment of numerous diseases. The talk on tuberculosis should emphasize the means by which the disease is spread and methods for its prevention, calling to their attention the dangers of careless spitting, sneezing, coughing, etc. The importance of having the disease recognized in its early stages should also receive special consideration, not only because early diagnosis favors the patient's recovery but also because the disease can at that time frequently be arrested before the individual becomes a source of danger to those with which he is associated at home and in the shop.

The talks may be delivered in the form of lectures, placards, leaflets or articles in the house organ, or small exhibits and moving pictures may be employed to bring the facts to the attention of the workmen in a forcible and striking manner. The local tuberculosis societies, where such exist, may be relied upon to assist in this work.

For the successful prevention of tuberculosis it is imperative that these talks should not be confined to the discussion of the means to prevent the dissemination of the tubercle bacillus, but, as already outlined, should include instructions in general hygienic measures.

In the industrial plants these talks might be augmented by such subjects as accident prevention, or the interest of the workmen stimulated by selecting such topics as are of special importance in the individual plant, emphasizing those occupational diseases which may possibly be peculiar to that industry.

While reference has been made to the workmen in all the foregoing statements it is equally important in the conducting of such a campaign that the employer of labor be also educated along these lines of public health. It may be that the campaign must first be directed toward this individual or group of individuals befor it will be possible to carry it out in the plant. To bring this effectively to the head of the plant, personal interviews will be absolutely essential.

Aside from the educational campaign outlined above the chief interest of the industrial physician lies in

the early detection of tuberculosis among the workmen. This is so important and presents so many interesting problems that it will be considered in more detail than has been accorded the other phases of this general subject.

If the campaign against this disease is to be effectual and meet with the success that our efforts should encounter, it is absolutely essential that the cases be discovered while still in the early stages. There are several reasons why this point is so important. In the first place, if the disease can be recognized before there is any extensive breaking down of the process and arrested in this stage, it is possible to prevent infection of the other workmen who come in contact with the individual affected. Second, it is equally essential from the standpoint of the workman himself.

The preservation of the working capacity of the individual affected, or possibly even his life, is almost absolutely dependent upon the early detection of the presence of disease. This fact is well illustrated by the chart recently published by the Prudential Insurance Company of America,[2] based upon a study of 69,500 cases, showing the results of sanatorium treatment in cases with varying degrees of involvement. Among the incipient cases, in 34.0 per cent the disease was apparently arrested; in 25.1 per cent it was improved; in 30.0 per cent it became quiescent; while in only 10.3 per cent it failed to improve and 0.6 per cent died. Among the moderately advanced and the far advanced cases the results were not nearly so good, the proportion of apparently arrested cases falling to 4.1 per cent and 0.5 per cent respectively, the unimproved increasing to 17.6 per cent and 29.7 per cent, and the deaths to 4.1 per cent and 33.0 per cent. This is well illustrated in Table I which is drawn up from the Prudential Chart previously referred to.

2. Journal of Outdoor Life, January, 1922, p. 30.

When Prognosis Is Good

On the basis of Table I it will be seen that the prospect of arrest of disease is very good among the incipient cases (1:3), but is very poor in the moderately advanced (1:24), and is almost nil in the far advanced cases (1:200); while death occurs only rarely in the incipient cases (1:166), occurs more frequently in the moderately advanced (1:24), and is very likely among the far advanced (1:3).

A study of this table also reveals a point which is worth while mentioning as it illustrates how inadequate are our present methods in the early detection of the disease. It will be seen that while only 15,807 incipient cases are reported, there are 28,138 moderately advanced, and 25,484 far advanced cases. In other words only about 22.9 per cent of the cases sent to sanatoriums are in the incipient stage, while approximately 40.5 per cent and 36.6 per cent, are already in the moderately advanced and far advanced stages respectively. If our present methods were adequate and effective there should be a much greater proportion of incipient cases being placed under sanatorium treatment than this table suggests as now being the case.

There is another factor which must be considered in a discussion of the early recognition of the disease and that is, that the earlier the discovery of a case in the incipient stage of the disease the shorter is the time usually required to bring the patient to a point where the disease may be considered as being arrested, the less time is lost from work. In the majority of cases this element of time necessary to secure recovery is

equally as important as that the man regain or preserve his working capacity, and this again is almost as essential as the preservation of life.

Granting that the importance of early recognition has been demonstrated, the question remains as to what is the most efficient method to pursue in order to secure this early detection of the disease. Several plans have been tried in the past which were based upon the employment of entrance examinations combined with a re-examination of those workers in which either suspicious signs were noted at the entrance examination, or in which suspicious symptoms subsequently developed. The detection of these suspicious features being left to the nurses, foreman, or fellow workers of the individual, or to the physician himself when the man comes under his observation on account of injury, reporting for illness or some similar reason. While this plan possesses certain features which would recommend it to the heads of the plants and those interested in not having the running of the plant interfered with by frequent examinations of the employees, it is too haphazard to be considered as an efficient or comprehensive method from the standpoint of prevention.

While undoubtedly a certain proportion of cases of tuberculosis will be discovered by this method, they will in many instances only be recognized when the disease has become fairly well advanced, when they can no longer be considered as being early cases. When this disease has reached a point where its presence is apparent to the laity, on account of the general symptoms and appearance of the patient, it has usually reached a fairly well advanced stage.

The truth of this statement was very clearly established in a general examination of the 5,706 police and firemen of the City of Philadelphia recently conducted by the Henry Phipps Institute, in which nearly two-thirds, (64.0 per cent), of the cases of tuberculosis discovered had never been previously suspected, even by the individual himself. The proportion of unsuspected cases showing a gradual decrease as the extent of involvement or definiteness of the lesion increased, the proportion of unsuspected cases being very high, (93.1 per cent), among those with early or questionable lesions, and only moderately high, (56.2 per cent), among those with well developed disease.

This survey of the police and firemen was carried out by the Phipps Institute with the object of determining the incidence of defects to be found in a group of this kind, the data obtained to be used as an illustration of the value of health examinations; to furnish us with information as to the best methods to employ, the cost, time required, etc.; and to perfect an organization to conduct such examinations. The purpose of the study was the development of an industrial department which would be prepared to conduct health examinations for the industrial plants in and about Philadelphia, and to furnish them with a diagnostic clinic to which could be referred such cases as the industrial physicians felt required advice from men who had had special training and experience in their several branches of medicine and who had access to special diagnostic facilities.

We have at our command a method for the early detection of tuberculosis which is as efficient and satisfactory as any we can hope to develop in our present state of knowledge. A well organized system of complete physical examination of all applicants for positions, with a careful adjusting of the work to suit the fitness of the man, combined with

periodic health examinations of the entire working force affords an efficient means of detecting disease in its earlier stages, provided the intervals between the examinations are not too long. I have been unable to secure any data which will accurately establish just how long this interval should be. Most of the plants employing periodic examinations perform them at intervals varying between one month and three or four years. The very short intervals were employed only when the occupations were extremely hazardous, as in chemical plants. It would seem that they would be most effective in any general plant if conducted annually.

When we refer to these examinations it must be understood that reference is made to a complete, general physical examination, as any examination which would be carried out for the detection of tuberculosis alone would be both inadequate and impracticable. The expense involved would not warrant such studies for the detection of one disease alone, and it is just as important in the prevention of this disease that defects of all kinds be recognized and corrected as it is to discover signs of tuberculosis. The prevention of the development of tuberculous disease depends upon mantaining the general health of the workman at the highest possible level, which would be impossible if defects of various kinds are permitted to pass unrecognized and uncorrected.

While the periodic health examination is an essential if disease is to be detected among workmen at a time when remedial measures promise the best possible results, they must be combined with entrance examinations of all applicants for positions if the prevention of disease is to be really effective. From the standpoint of tuberculosis the entrance examination serves as a means of detecting individuals who are suffering from active disease, cases which should be at rest under treatment and not performing work of any kind if their health and life are to be preserved. These men are also possible sources of infection to the other workmen and should be rejected as a safeguard to their own health and to that of the other workers in the plant.

But the rejection of unfit and dangerous cases is not by any means the most important function of the entrance examination. In the examination of a large number of applicants a certain proportion of them will be found to be below par, possibly suffering from defects which it may be impossible to correct but which will not seriously interfere with the working capacity of the man as long as he performs work for which he is fitted and which will not tend to aggravate his disability. For example, a number of men will be discovered in which evidence may be present which points to some defect of the lungs, signs suggesting pulmonary disease, including those cases, so difficult to evaluate, with signs of slight contraction or fibroid change at one apex or both apices of the lungs. These cases often may be below the normal weight for their height and age. The selection of the kind of work these men may be permitted to perform without the risk of their pulmonary defect becoming an active disease process requires the exercise of the greatest care and judgment on the part of the examining physician. While probably the large majority of these cases may perform work of a proper kind under suitable conditions with perfect safety, they should not be assigned to any position which would expose them to such industrial hazards as dust, dampness, poor ventilation, great variation in temperature, or be allowed to undertake heavy manual

labor. The entrance examination is more important as a means of fitting the man to the job than as a barrier to the unfit or dangerous workman.

Any discussion of the function of the entrance examination is incomplete without some reference to the classification of occupations in industrial plants, which has recently been receiving some attention, and which, if carefully planned and defined, would materially assist the work of the examining physician. Any classification of occupations must be made with the greatest possible care, with due consideration of the defects most commonly encountered and the effect upon them of every industrial position. While this is sufficiently important to receive the earnest thought and study of every industrial physician, the subject is too involved to discuss in detail in a general paper of this kind.

The phase of this subject which is of most interest and the greatest practical importance to the physician engaged in making industrial examinations is that relating to the diagnosis of tuberculosis. He is most interested in securing information in the direction of aiding him in the determination of what cases should be considered as suffering from tuberculous disease, which cases with signs of pulmonary defects might still be accepted for employment, and what signs should be looked for in the reexaminations as indicating the development of disease. For the physician to judge these cases with any degree of accuracy it is absolutely essential that he be thoroughly familiar with the manifestations of the disease, its varied clinical types, and the physicial signs and symptoms which indicate its presence, and, what is equally important, its degree of activity.

Contrary to the very general belief, this does not necessarily mean that every examining physician should be what is generally termed a "tuberculosis expert." It does mean, however, that he must carefully and thoroughly examine every case coming under his observation. More cases of tuberculosis pass unrecognized because of lack of care and thoroughness in the examination than are missed because of inexperience or ignorance on the part of the physician. The examiner must be constantly on the alert for the possible presence of tuberculosis in every case, regardless of his general appearance or state of nourishment, and he must be familiar with the signs and symptoms which suggest its presence. If he does not feel qualified to make a final diagnosis in questionable cases he should arrange to have these cases studied by someone possessing special knowledge, with access to diagnostic measures which the general physician does not possess, either by sending these cases to the specialist or by having him visit the plant.

The discussion of the physical signs and symptoms is too large a subject to consider here in detail, but reference might be made to a few signs or symptoms which may be obtained with very little effort and would assist in indicating which cases should be most carefully examined for the presence of this disease. In our examination of the police and firemen previously mentioned it was found that the presence of such signs as underweight and low blood pressure may be looked upon as signs of suspicion, and the cases with these signs should receive an examination of chest which is more thorough and exhaustive than it is practicable to give to every case. This must not be taken to mean that the chest of all others may be ignored or examined superficially, but merely that this special group should receive an ex-

tra amount of time and study. (This question has been considered in detail in a previous article of the present writer, which is to appear in the *Journal of Industrial Hygiene*).

Summary

The industrial phase of the tuberculosis problem may be said to consist of three principal divisions, namely: (1) improvement of plant hygiene; (2) education of the workman in regard to preventive measures and in regard to improved living conditions; (3) the institution of entrance examinations combined with periodic health examination. Preventive efforts directed along these three lines, if intelligently and competently executed, may be relied upon to secure results which will materially reduce the loss of time, efficiency, money, and life for which this disease is responsible in every industrial plant and in every group of workmen, and which would be reflected in an improvement in the general health of the public.

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THE SIGNIFICANCE OF MEDICAL RESEARCH* FOR PHILADELPHIA

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The developments of a century, and particularly those of the forty years just past, have conventionalized a popular conception of medical research. The discovery of vaccination against small-pox by Jenner; the epoch-making fundamental discoveries in bacteriological method by Pasteur and Koch; the discovery of diphtheria antitoxin by vonBehring and the results of its application; the names of Sir Almroth Wright and of Col. F. F. Russell linked with a successful vaccination against typhoid; of Ehrlich and Salvarsan, of Reed, Carroll, and Lazear with Yellow Fever and the Panama Canal; of Flexner with Cerebrospinal Meningitis and Poliomyelitis; even perhaps—so rapidly is the work of medical laboratories now translated by the popular press—the name of Noguchi may be in your minds connected with Yellow Fever as the final discoverer of the cause of this disease; this conventional conception of the subject is no doubt present in all your minds in outline or in clear detail, as the case may be.

The conventional forms and devices of art are better suited to the more static materials and structures. The durable walls of buildings and memorial monuments are properly decorated with carved wreaths, the figures of Greek gods, or the names of men and women long dead. Our civilization as it develops from day to day is the farthest removed from the static—it is dynamic, frequently to the danger point as we all know—and among the components of this dynamic modern civilization, none is more fluid than scientific research—that in the field of medicine being well forward in point of mobility.

There is much, I think, to be said on the subject of medical research which is not included in that conventional aspect which is, as I believe, well known to you all. I wish to turn your thoughts for an hour to some of these less frequently considered, less obvious aspects of the subject.

Allow me to return to my title for a moment and perhaps you wonder why I think the subject has anything in it of peculiar interest to Philadelphia. Certainly as you have appreciated the improvements in medical practice based on our increasing knowledge and skill, they have seemed to you to be shared equally by the whole of humanity. Doubtless these advances have seemed as much yours by divine right as the air you breathe. How are you, as residents of Philadelphia, differentiated with respect to this question from those living at Harrisburg or Wilkes-

* A public lecture delivered under the auspices of the University of Pennsylvania at the foyer of the Academy of Music, Philadelphia, January 17, 1922.

Barre, Trenton or Princeton? You certainly share with them, for the most part, the benefits derived from vaccination and the improvements in the diagnosis and treatment of diphtheria.

But if I were speaking of the local significance of scientific research at Princeton, for example, I should be speaking to a University audience in a town almost wholly University in its interests. The local question of interest would be the relation of the University and research. I could go little further. In Wilkes-Barre or Trenton there would be little or no occasion to speak of the relation of medical research to medical education. One would point his remarks doubtless in part to the changed conditions of medical practice with advancing knowledge. One would doubtless speak of the importance of studying with care the influence of particular occupations, coal mining and pottery making, on health and on the incidence and cause of certain diseases such as tuberculosis or pneumonia; on the peculiar damage done to the lungs by constant exposure to mineral dusts. In Harrisburg one might naturally emphasize the importance of the subject to all the citizens of the state, the complete propriety and the prime importance of liberal legislative appropriation for scientific research, with emphasis on that in the medical and related sciences. Going still farther into the country, the questions of rural hygiene, rural occcupations, and the practice of medicine in the country districts might be expected to excite immediate and local interest.

But you in Philadelphia (perhaps after eleven years of consecutive residence I may be permitted to say, "We of Philadelphia"), are a community of nearly two million souls, a modern city of a magnitude comparatively new in the world, and by that very fact presenting new problems in medicine and hygiene, new opportunities and fresh necessities. We are possessed of a large and influential University, a part of which is the oldest medical school in the country, a University which cultivates as well all the sciences contributory to medicine. We have other medical schools of the first rank, and are responsible for the training of men and women who will practice medicine the world around. A large industry and a tremendously diversified industry presents problems of medical and hygienic management and problems of the origin of disease of great complexity. An industry, in part much concerned with the manufacture of drugs, chemicals, and biological products used by doctors all over our country and in many other countries, is part of our life. A diversified population presents for consideration the racial aspects of disease. A great port, with contacts with all parts of the world, gives rise to problems of quarantine important to us and to our country.

How then can we take a more or less placid, cheerfully and irresponsibly accepting, attitude toward medical research which is the understandable attitude of many people less fortunate by circumstance and situation?

Before proceeding I do wish, however, to develop one phase of the subject of research in the field of science which has general rather than local significance.

Mr. James M. Beck, in a recent article entitled "The Age of Lawlessness" (Current History, Oct. 1921) attempts to account for what we hear much of in these days as the spiritual bankruptcy of our times. Features

of the supposed social degeneration are said to be a general revolt against authority as evidenced by strikes, revolution, sovietism, bolshevism—second, third, and fourth are aversion to labor, class hatred, mass morality—evidences of a mechanical age, devoid of character and stamina.

Though we disregard the extremes in this indictment and without making invidious comparisons with other ages (the better times of the "good old days") we must still acknowledge that there is much room for improvement. We all dread anarchy, recognizing that individualism carried to the extreme of refusing co-operation would make impossible the life together of any considerable number of people on this earth. We are equally fearful of communism with its threat of submerged individuality and its probable lack of incentive to effort. We trust, and believe we have demonstrated reasons to trust, a "live and let live" principle of life in which, in considerable measure, virtue and individual effort bring their own rewards—often large rewards—and in which forcible restraint is exerted only on those who refuse to recognize the "let live" as a vital half of the formula.

Scientific research here takes its place as one of the great social forces of our day. Like religion, it is a great stabilizing and conservative force which tends to unite people in a common way of thought and effort. Moreover, it is one of the great constructive forces. It compares with the great impulse to migration and colonization in its direction, enabling us to make better use of all our world resources. But as compared to these, research looks into the future to the time when the possibility of occupying new ground will be exhausted. It is opposed to communism, as no real result is to be anticipated from research except as the expression of a very high degree of individual effort. In this particular it is only less extreme than the fine arts—literature, sculpture, and painting. It is, however, definitely less extreme in that, as the technical requirements of research become more involved, co-operation becomes an essential to success. The need for and effects of co-operation might be emphasized; for the moment I make the point that actual achievement in science is inevitably an expression of individuality in conception and effort, and most often an evidence of the ideal of work for the sake of work.

I have, I think, covered the general points necessary for a mutual understanding, and now wish to proceed to the topic of the hour. The first point I wish to make with you today is that, based upon these last mentioned general cultural considerations of scientific research, medical research has a peculiar significance to us as Philadelphians. It means contact with and renewed respect for a distinguished past.

The men who first established medical work on a self-contained basis in this city were men who had availed themselves of the best contacts the times afforded. They had been to England, Scotland, Holland, and Italy. They had known John Hunter, the foremost practitioner and the foremost medical scientist of his time, and other leaders—very able men of that period. They returned here fired with enthusiasm for learning and for teaching; they met with sympathy, and the medical school at the Pennsylvania Hospital was the result. Their efforts sufficed to accumulate a library good for its time, to form an organization capable

of teaching the fundamentals of medical practice to the young men who came to them. They did not, however, succeed in advancing far beyond the teaching they had received. It is no reflection on them that they did not, for the demand upon them for immediate practical results must have been most insistent. They were the associates of the men who were making a new world by fighting for it, and had to take their full share in the revolutionary and pioneering activities of their time. So, while a genius like Franklin, not a doctor, was making some contribution to medical technique and even to medical thought (my friend Dr. William Pepper tells me that Franklin was the first man to construct bi-focal lenses, that he believed in the infectiousness of common colds, and strongly advocated open windows in sleeping rooms, that he made a flexible catheter, and was probably among the very first to attempt the treatment of disease with electricity), while some of the group were proposing radical changes in practice (Rush was far ahead of his time in his ideas with regard to the management of the insane), still no positive advance of our knowledge of the principles of medicine is to be attributed to the men of that period in Philadelphia.

Some half century later, in 1837 to be exact, Dr. William Wood Gerhard used the facilities for study which had been developed in making a scrutiny of the fevers prevalent here. In the wards of the Pennsylvania Hospital, he was able, for the first time, to make a clear distinction between typhoid fever and typhus fever. This differentiation was difficult at the time, although easy enough in the light of our present knowledge. It has remained, perhaps, the most outstanding of all Philadelphia's accomplishments in the field of medical research.

Considering the matter less rigidly, and confining our discussion to those who have passed beyond, Philadelphia again has a proud record. Wood, Mitchell, Gross, Meigs, Leidy, and Pepper are family names which stand here and the world over for developmental work in Physiology, Pathology, and practical medicine. It remains a constant source of conversational matter and argument whether progress is more fitly marked by outstanding accomplishments or by the multiplicity of sound observations and methods developed piece-meal which together make up a new conception or procedure. Judged in either way, Philadelphia of the past has been a center with a highly cultivated medicine, and likewise from either the immediately practical or from the strictly research point of view. It is a commonplace to you that Philadelphia has been a great medical center with a broad outlook and a world-wide influence.

Probably Philadelphia is today a great medical center, no less a one than in the past. This question I have no wish to discuss even were there ground for a decisive discussion. I am interested in the future. Is our city to retain, or if you choose, to again acquire a commanding position in medical thought, science, and practice? I have said enough to show that if the future holds this for us, it will be to us somewhat more satisfying because we will be maintaining a great place which is ours by tradition and, per contra, if this place is not held we will not easily escape the reputation of having wasted a substantial birthright. This is the first of those meanings which medical research has for Philadelphia which we do not share with all the world.

Another potent meaning for us is to be found in a quite different direction, and is of a much more practical nature. I refer to the better medical service which you and your neighbors will receive if we cultivate research rather than neglect it.

That such better service will result can be asserted but is, it must be admitted, scarcely susceptible of proof. I maintain the following reasons for the assumption. The research man is better able, often, than his practicing colleagues to judge of the evidence underlying new proposals, is most apt to have a highly developed critical faculty, and to have greater confidence in his critical judgments. He is quite used to looking for the "bug under the chip" and loses nothing in prestige if he exposes it when seen. On the other hand, he has a higher respect perhaps for precise technique and is apt to have greater confidence in recommending the trial of new procedures which, after critical examination, appear to be well grounded. In the trial of new procedures there is most often demanded great precision of application in accordance with carefully determined conditions, and those who have had experience with precise work in uncharted fields are most apt to be good judges. The spirit of these men reacts on their practicing colleagues, they are consulted and looked to for advice, suggestion, and criticism. Good new things are implanted on a community more quickly because of their interest, the false alarms are in some degree avoided.

Moreover, a large number of the medical students who graduate from the schools of this city settle here and serve you as your medical advisors for the remainder of their lives. Probably nine-tenths of the men practicing medicine in Philadelphia have always been and will be graduates of our local schools. In the past many of these men have gone elsewhere for post-graduate study and experience before settling down, and this also will doubtless continue to be the case. It should be so. I now venture the assertion that these men will be better able to advise and assist you with your bodily ailments if they have had close contact with men who are actually doing research work and who may be expected to inculcate the spirit of independent observation among their students and friends. The practitioner group may be expected to acquire something of the research spirit.

Now I am far from putting forward the proposition that the out and out research man makes the best practitioner of medicine. It is certainly true that a very hopeless type of medical advisor is the man who has spent a year or two doing a research to acquire a reputation and then forgets the experience entirely in his anxiety to build up a business, or forgets everything about it except its advertising value. On the other hand, no one has ever been a through and through good doctor who has not had the instincts, the mental aptitude, the attitude toward life of the confirmed student. I use the term student here in a broad sense, not confining myself to bookish men but including anyone who has a respect for and thirst for fact as opposed to surmise. The students who go into medicine today naturally turn to research—laboratory research most often at first, as the best place to gratify their interest. If they are fortunate enough to make a contact for a year or several years with an accomplished man and a good problem, it must affect their whole atti-

tude for life. And it must affect it favorably for you, in that it will make them intelligently interested in acquiring new methods and intelligently critical of both the old and the new. Authority, whether imposed by the elder practitioners or by the laboratories is, in itself, a poor basis for treating sick people. Your consistent appreciation and full support of the research interests of your medical schools will then bring you—bring Philadelphia—a substantial return in the character of your medical advisors and have a profound influence for the better on the quality of the work they will do for you.

What I have said of the influence of medical research on the daily work of the practitioner of medicine applies with much more certainty and force to your public health officials. Almost the whole activity of health officials, so far as it is directed toward preventing disease, and more and more their activities are so directed, is based upon our knowledge of diseases acquired by research since the year 1875. The health officer performing his proper function is your doctor of prevention.

Our newer knowledge of infectious diseases and the consequent demands for action forced the rapid development of departments of health; men qualified by training and experience to make the most of these developments were, of course, not immediately available. Almost any interested doctor was, if the friend of the appointive power, considered qualified for this work. Operating surgeons have been much favored in our community. But of recent years—through our experience in the tropics, with the Panama Canal, and the Philippines, and now with the war—there have come to be men with a wide knowledge of disease and an extensive practical administrative experience covering the methods of prevention. We are fortunate in having as our director of health one of these men, scientifically qualified and, from the point of view of administrative experience and courage, on top of the job. But, given all these qualities, a man in this position requires public opinion at his back and the support of others who share his knowledge and point of view. To a great extent he can rely on the medical profession for the support he requires. This is because the members of the profession almost always recognize that they are citizens before they are doctors, and are governed by a self-effacing public spirit.

There is always, however, a conflict of interest; the practicing doctor feels required to protect his patient from official annoyance so far as he is permitted. Reporting of infectious diseases, births and deaths, and the official review of his reports which follow, means labor and trouble for him, and he is bound to be conservative in the face of new suggestions. The Public Health Officer is likely to be most effectively advised and supported by the research group among the medical men in the community where such a group is present; and those communities are more fortunate than others. This may be a matter of opinion but I have not the slightest doubt that my opinion as expressed would be agreed to by all with first hand knowledge of the matter.

If what I have said is true of the governmental agencies, it is much more true of what may be designated the voluntary health agencies of the community, and these in Philadelphia are many. Tuberculosis societies, societies for the prevention of mental diseases and cancer, vice commissions, child welfare organizations, organizations to further and

control the use of milk, all these are seeking to impress on the community and on the official departments the need for more measures and for new measures. They often seek to investigate conditions, to devise new procedures, and to install them in the community operating scheme. These agencies are tremendously important for they really make public opinion in health matters. With few exceptions, they actually originate nothing, in the broad sense of the word. They take something originated by students in the field of their endeavor and try its application; try to put it in practical form for use. It scarcely seems necessary to point out that much of this activity is troublesome or mischievous if not carried out within the spirit and the true meaning of fundamental facts. You will spontaneously have recalled what I said of the critical faculty of the research man and will agree that he had best be consulted wherever and whenever possible in connection with the investigative activities and the administrative proposals of these voluntary agencies, and that Philadelphia will be in a better situation to profit by these endeavors if research men are locally available, to be drawn upon freely in this connection.

The thesis, then, which I have advanced under cover and tried in some measure to defend before stating it in its bald entirety, is that Philadelphia and you its residents share, as a matter of course and common knowledge, in the direct advantages to be derived from successful medical research wherever conducted. That you have so profited is evidenced, for example, by the progressive fall in your death rate and the correlative increase in your expectation of life. You are in a position to profit with the average of humanity by forwarding science as one of the great cultural forces of our time. If you forward science, medical science particularly, you will derive great additional advantages by reason of the presence of the necessary machinery and personnel as a part of your fully developed community equipment, and you are in a sound position to do this because of what you now possess to build on, a possession held by few cities.

It would be gratuitous, even were I able and supposing that I had made my first point with you, for me to try to develop a program of the consequences deriving from this line of thought. But, granted that you have been interested to follow me thus far, you may permit me to make briefly certain casual suggestions as to the nature of some of the resulting considerations.

Proper pride in our local medical schools and in our University is one of them. Especially in our University's scientific departments, in the research achievements of our University's school of medicine and in the accomplishments of a similar nature in the other medical schools and hospitals of the city; pride in their past, still more pride in helping them to a future of a similar distinction. We may have a creed, we may have local affiliations of a social nature, but science affiliates with only the intellectual attainments, the spirit for work, and the physical equipment with which its practitioners are surrounded. You may then, in the interests of economy of money and effort, look with sympathy at reasonable efforts to centralize effort, and your University is the proper place for the effort to be centralized.

During the past fifteen years there has been a very vigorous effort to improve the quality of education furnished to medical students, the practicing physicians of the near future. We have shared in this effort so far as circumstances seemed to permit. The country over, old schools with no intellectual and little moral or financial background have been closed, schools with a better start or better background have been revivified, in some places schools have been merged, and some new schools have been opened. Without comparing our situation with any other, I content myself with saying that this renovating process, so far as Philadelphia is concerned, is far from finished; in many respects perhaps it has scarcely begun. But it is being done; in the words of our forward-looking citizen, Mr. Bok, "It can be done." No one can see today all that is involved. The bill cannot be written but it can be seen that it will be large.

How is the bill to be paid? There are those who think the state should pay it; there are those who think private interests should pay it. The bill will be large enough to demand all that both state and private interests can produce—at least that is my opinion. Moreover, help will need to be sought from the wealth of the country at large as it is made available through the great philanthropic foundations. It will doubtless be proper to expect help from them and to accept it when forthcoming, always remembering that the Lord helps most those who have a plan and show that they intend to help themselves towards its execution.

This financial aspect of the matter is an incident which is not our real concern at this moment. The main point is that in this rebuilding of our local machinery for teaching medicine, the considerations I advanced in the earlier paragraphs take very concrete form.

There has been much debate in the past between those who believe that teachers of medicine need be nothing but school teachers using medical books for texts, with their practical experience for illustration, and those who think that teachers of medicine must themselves be research men. The debate still continues here and elsewhere. Those who have followed me will sympathize with the words of a teacher friend of mine who takes his obligations to his students most seriously. "Teachers of sciences fundamental to medicine today (pathology, physiology, anatomy, chemistry, and pharmacology) are teaching the results of the researches of the last hundred years. It is difficult to see how they can teach what they do not understand and how can they understand if they have not the spirit of research in themselves. If they have this qualifying spirit they will, of course, be quite unwilling to teach unless adequate facilities in buildings, budget, assistance, and time are also provided for the pursuit of studies in which they are primarily interested."

To those of you who are outside the walls of the medical school, this latter attitude may not be altogether understandable. Why should men who are employed as teachers be so expensively exacting in a somewhat different direction? There must be taken into consideration the fact that when these men undertake to exert themselves in the field of medical research, they not only enter a field of extreme difficulty in the technical sense, realizing that recognition for their work will be very hard to attain by reason of this, but they voluntarily renounce, in accordance with a

strict code of ethics, every opportunity to make material profit which might be expected to arise from a life of study and experiment. Other fields of research offer the gamblers chance of happening on to practicable things which, when patented and developed, bring rich rewards. As I have said, all this is outlawed in the medical field, and the rewards must come from the work itself. Naturally those who follow this line can do no other than be exacting as to the reality of the resources put at their disposal.

More and more, also, those interested in other lines of practical work are becoming interested in this method of approach to the teaching of their subjects. Leaders in engineering, for example, are now beginning to talk of the advantages to their profession and to the public which might be derived from making the engineering schools centers of research—liberally supported for the study of the abstract problems of science underlying their work.

Our line of argument suggests, then, continuous endeavor to keep the most adequate support available for the research activities of the medical schools and their associated hospitals.

You will also want a co-ordinate development of a great school of hygiene, preventive medicine, and public health as a part of your community equipment. Returning to my remarks on the relation of research men to the official and unofficial health agencies, and appreciating that this field is much less systematically developed than that of curative medicine, you will understand my feeling that research is, if possible, an even more necessary adjunct to the teaching in such a school.

The University has successfully inaugurated a post graduate school of medicine on somewhat different lines from any previously thought possible. The idea underlying the present success is that the practicing physician who wishes to improve himself needs most of all to review his fundamental teaching in the light of his practical experience and, secondarily, to be made acquainted with the advances in method since his graduation. Eventually there will be needed here a strong research influence among his teachers if the most is to be accomplished.

What I have so far said leaves quite out of account one of the most striking developments in the field of medical research. I refer to the establishment, during the last twenty-five years, of numerous funds, institutes, and foundations whose purpose it is to promote scientific research in medicine as a first purpose. Of these, the most conspicuously successful has been the Rockefeller Institute. Founded without restriction to any special subject, the Institute has been so well supported financially, and so well managed as a venture, that it has been able independently to enter upon the study of many of the special subjects in medicine with success. Chemistry, physiology, and the various infectious diseases, have been approached with resulting increases in our knowledge, and life saving improvements in practice have developed. Money and good management have combined to create an organization which in strength of personality exceeds that of the scientific departments of most medical schools, and research is its only purpose. Before and since, in point of time, other organizations with similar aims have been founded. These have been more restricted in resources and often in purpose. The ma-

jority have been created under the control of some existing university or have, in course of time, come under such control. They have, some of them, been free to enter any field of medical research. Others have been definitely restricted to a narrower range. These have been explicitly founded for the study of cancer, tuberculosis, infectious diseases, or chronic diseases, as the case may be, or when not so restricted in actuality, the terms of the gifts have often created a moral obligation which has amounted to a restriction.

Our University has under its control and management four such funds. A consideration of them is of interest in connection with our subject. The fund which last became active is the Duhring Fund for the study of dermatological subjects. This is an adjunct to the teaching in the department of Diseases of the Skin and, for that department, fills the need for research support for the teacher of which I spoke in earlier paragraphs.

The John H. Musser Foundation for Research Medicine serves much the same function in the department of medicine, and is likewise a connecting link between the fundamental sciences and the science of clinical medicine.

The Wistar Institute for Anatomy is on a different basis. Its function is to support a public museum and to conduct research in anatomy. The staff are prohibited from undertaking teaching in the medical school. The Institute was founded at a time when the general anatomical description of the human body had been fairly well completed. The staff have been well forward in the newer movement to relate structure to development and to function which has come to be the chief interest of specialists in human anatomy everywhere.

The Henry Phipps Institute has as its first purpose the study, prevention and treatment of tuberculosis. Related subjects may be considered. With respect to the Phipps Institute I could naturally devote another hour to telling you of its past and our ambition for its future. I do wish to give you an idea of some of the more general questions which arise from the conduct of such an Institute, its attitude toward its special problems and its usefulness to the community in which it works.

Comparing the outlook of men working in an institution devoted to medical research generally speaking, and one restricted to the consideration of one disease such as tuberculosis, your first thought is probably of a limited problem requiring only limited resources, and giving rise to a limited vision. And this is the immediate result to the outlook of one entering upon the work of such an institution. Quickly, however, it is apparent that neither chemistry, physiology, nor any other fundamental science considered generally, furnishes the special information which one needs for a real understanding of such a disease as this, and one feels the urgent need of establishing special facilities for study in many quite unrelated fields. The urge to expansion, the demand for increased resources becomes pressing almost as soon as in the case of the Institute more generally oriented and is, perhaps, more severe because of a feeling of especial responsibility imposed by the direct mandate to study a serious practical problem. There is in principle, then, no limitation on the development which such foundations may require. Practically, how-

ever, restriction of subject does restrict the number of interested workers, and we cannot always grow with our ideas or with our resources because we cannot find interested and capable collaborators to meet each demand as it arises.

Tuberculosis occupies a peculiar position today in the research field in that it is surmised that its prevalence may be much influenced by social and economic conditions. Aside then from the questions which are properly the subjects of inquiry in the departments of a medical school or an Institute for Medical Research, Dr. Landis and others of our staff have naturally become greatly interested in what may be spoken of as social medicine.

We find, as others have, that precise researches in this field are tremendously involved, that they are time consuming and expensive. One inevitably becomes aware of conditions, bad on any account, which seem to demand reformatory action. We are thus led directly to a position in intimate contact with the every day life of the community—of the people of Philadelphia.

You may see a complication here. How far is it consistent with our place as a part of your University to take active steps toward seeing that your houses are rebuilt to conform to the requirements of the law, or that they may be made better than the law requires? If that is a university function, how should it be performed? You may see from this example (I have purposely chosen one that does not press on us at the moment) that our presence may give rise to some thoughtful argument in the governing bodies of the University. It emphasizes my previous point that research has a more intimate meaning for you than you may have realized. And in conclusion it enables me to say wherever in our consideration of the intricate and difficult problems of support or policy we have had occasion to ask the interest of the University authorities, the medical faculty, the people of Philadelphia, and those outside of our city who are interested in health problems, our reception has been most considerate. I feel quite secure in the belief that this newer development in medical research, the extensive support and conduct of research with a special purpose other than that related to its pedagogic relationship and value, has a place in Philadelphia which will in the future be recognized on appropriate occasions and in suitable ways and, I hope, to your material and spiritual advantage.

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THE RELATION OF HEREDITY TO TUBERCULOSIS

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Notwithstanding this subject is very old, one may hope to add some new evidence bearing upon it and to indicate that such conclusions as the profession may possibly have come to are properly subject to revision.

From the beginning of medical time it was considered that tuberculosis ran in families; that heredity had much to do with the occurrence of the disease. With the discovery of the tubercle bacillus and the realization that tuberculosis was due to an infectious agent, it came to be believed that probably hereditary influences were more apparent than real, and that individuals in certain families more often had tuberculosis, not because of any special influence of blood or breeding, but because the disease having been established in that family, the chances for contagion and contact were much increased, and all facts could be explained in the light of our knowledge of tuberculosis as an infectious disease.

Since the establishment of the infectious nature of tuberculosis, a certain amount of work has indicated that possibly there was something more to the matter and that the older view could not be lightly dismissed.

A number of years ago Dr. Pope went over all the material then available at the Saranac Lake Sanatorium, making a tabulation of this material on the basis of relationships of patients, in order to find out whether husband or wife were more liable to contract tuberculosis from each other than were the children of tuberculous parents. This material was collected and taken to England and put into the hands of Pearson who was interested in the study of this kind of material. Pearson applied mathematical methods to the study and seemed to show to his own satisfaction that there was evidence of hereditary influence on the development of tuberculosis in this material, namely, there was certain evidence that the marital relatives contracted tuberculosis in a larger degree than the average population considered without reference to the incidence of tuberculosis in the marriages.

There was also a larger influence evidently due to the blood relationship; that is, the children of tuberculous parents were not only more liable than the average population to have tuberculosis, but were more liable to have tuberculosis than the husbands of tuberculous wives or the wives of tubercu-

lous husbands. There seemed to him a satisfactory evidence that blood had something to do with it. He reasoned that the chances of infection were as great between husband and wife as they were between parent and child. These results of Pearson's, however, have not been generally accepted by medical men up to date, and there are two reasons why this is so. First, from the fact that very few medical men were able to understand the method by which the results were arrived at and the terminology in which they were expressed. The second reason was biological, based on the proposition that most medical men thought that not sufficient account had been taken of the various susceptibilities to tuberculosis as they were here involved, and the fact was disregarded that children were more apt to be infected than adults, and this greater susceptibility to infection during childhood might adequately serve to explain the figures.

A pupil of Pearson's (Goring) undertook to restudy the same sort of material by taking prisoners in a certain English prison as the basis, and again it was found that children of tuberculous prisoners had tuberculosis in an appreciably larger percentage than the children of non-tuberculous prisoners. There was no difference discovered between the wives or husbands, as the case might be, of tuberculous prisoners as against the non-tuberculous. It was reasoned, then, that this had answered the objection cited in a fairly convincing way, because the prisoners are not much in contact with their families, either the marital relatives or the blood relatives, and there was an appreciable difference in favor of the proposition that the incidence of tuberculosis was higher when blood lines were followed. It is difficult to say what impression was made by the work of Pearson and Goring and what the prevailing opinion is in such a matter. Suffice it to say, the influence of heredity as predisposing to tuberculosis has been quite largely discounted by the members of the medical profession and by others whose opinion carried weight in public health work.

A great deal of work done in our laboratory has led us to the conviction that within any species of animal there is a large variation in resistance to tuberculosis. Rats and mice, which as species are very resistant, show a very wide individual variation also. Guinea pigs and rabbits as species are much less resistant, but also show a wide range of individual variation. The records of experiments with cattle indicate similar individual variation, and from what we know of tuberculosis in the human species, we may surmise that there are racial differences, but we may assume with greater assurance that individual susceptibility varies greatly.

We have tried to determine by experiment whether these individual variations had any true basis in heredity. The work has been made possible

by a coöperative arrangement with the Bureau of Animal Industry of the United States Department of Agriculture. Dr. Sewall Wright, of the Bureau's staff, is jointly associated with me in all that follows.

Some fifteen years ago the Bureau of Animal Industry at Washington studied certain problems in the field of genetics and heredity on the basis of experiments on guinea pigs. The problem they studied was: What is the influence of inbreeding on the general qualities of the animal? Does inbreeding, as many stock raisers maintain, inevitably cause deterioration, or does it not? To satisfy themselves on this point, they had started from twenty-three pairs of guinea pigs from which they had continuously bred by a very rigid system of brother and sister mating. The answer which they found was that inbreeding did not, of and by itself, cause deterioration. The primary effect is a fixation of character, good, bad, or indifferent. A different combination became fixed in each family. Families with an especially unfortunate combination did not long survive.

We have used five strains which had been retained from those older experiments to test resistance to tuberculosis. The system of brother-sister mating has been long enough in operation so that the strains are practically homozygous. They are found to differ by as much as 100 per cent in their length of life after standard inoculation with B. Tuberculosis.

The results suggest that the hereditary influence is exerted through at least three and possibly four factors or groups of factors capable of being transmitted separately.

It would certainly throw much light on the fundamental nature of natural immunity to tuberculosis if the physiological characteristics of these hypothetical factors could be determined. Our efforts in this direction have not as yet led to any decisive result. Dr. Wright's study of the Bureau records has shown that such attributes as age, weight, ability to gain weight, fertility, and ability to bring to maturity young born alive are, even when considered together, of slight importance as related to resistance to tuberculosis.

It may possibly turn out that more significance is to be ascribed to the suggestion which a recent experiment has developed, namely, that these guinea pig strains appear to differ in their reaction to a local tuberculous infection of the skin and in their reaction to certain inflammatory irritants, such as croton oil and cantharides. We have not so far been able to formulate an estimate of these differences in terms of resistance factors, and the matter is referred to only to show the trend of our further search for explanatory evidence.

How far is it useful or proper to go in the application of the experimental results so far obtained, to an interpretation of human tuberculosis? It is now generally regarded as true by biologists that wherever factors or groups of factors can be transmitted as units in heredity in one species of either plant or animal, those factors will be similarly under hereditary influences wherever they may occur. It is also recognized that when such factors are found in one species, they are very likely to be common to other related species as among mammals for example. There is, however, no a priori assurance that the relative importance of the factors will be maintained from species to species. There is, then, reason to expect that the factors influencing resistance in the guinea pig are also a human possession; until we can definitely recognize these factors as such and follow them into the human species by observation, we will be unable to dogmatize on their effectiveness as influences governing our racial reaction to tuberculous infection.

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FURTHER STUDIES ON THE COMPLEMENT FIXATION REACTION AS APPLIED TO TUBERCULOSIS[1]

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This paper is a continuation of a study of the subject begun by one of the authors (Lewis (1)) several years ago. It was then thought that some of the difficulties encountered in attempts to repeat observations reported by others might be overcome by consideration of the more fundamental features of the reaction. As the subject then stood, most workers were accustomed to ascribe their difficulties and their differences to the varying qualities of the antigens derived from the tubercle bacillus; each attributed his supposedly greater success to the virtues of his particular antigen. Critically examined, the literature at that time could hardly be said to show convincing evidence that a clearly defined, permanent fixation reaction could be obtained with any sera from cases of tuberculosis. By the methods current, only transient inhibition of hemolysis was secured in most instances; and it seemed likely that the fair agreement, which did as a matter of fact prevail among the published figures of the various authors, was in reality fortuitous. Our contribution to the subject at that time depended on an approach, through quantitative methods, to several of the fundamental factors concerned in any such reaction, with the conception that the fixation reaction need not necessarily develop in detail in strict accord with the Wassermann reaction which had been its prototype in the practical domain.

We were, in fact, able to show that the antigen-antibody complex bound complement more slowly where tubercle reagents were concerned than in the classical case developed by Wassermann. With the preparations then used and the system then employed, a four-hour period of primary incubation was found most suitable. When this time was used and when, further, several different tests employing slightly

[1] Read before the Pathological Section at the annual meeting of the National Tuberculosis Association, New York City, June, 1921.

different quantities of reagent were carried out simultaneously, so that minor variations were revealed, it became plain that with suitable materials a complete and durable fixation of complement could be obtained with constancy.

Series of tests were then carried out with human sera in an effort to apply the corrected method to the practical problem of diagnosis. In one series the complement was varied, in another the amount of antigen. While the individuals concerned were not the same, the result, by and large, was about the same. In general, about ten per cent of clinically nontuberculous persons gave a positive reaction, and a somewhat larger number of tuberculous subjects failed to react. Practically, our results did not differ materially from those of others, even though we felt somewhat greater confidence in the stability of the method as we had employed it.

Another step of a quantitative nature was then essayed. A number of the sera which reacted alike were pooled and mixed with an equal quantity of supposedly pure glycerine. After a number of months, these were found to be usable and over a period of weeks they seemed to be stable. These were used as the fixed point in a consideration of the qualities of the various antigens which had been proposed. Incidentally, it was also made out that an alcohol-soluble substance, having pronounced and apparently specific antigenic properties, was a common constituent of all the available antigens.

In the meantime Petroff (2) had proposed an extract of the tubercle bacillus in twenty-five per cent glycerine as an improved antigen, and Wilson (3) had advocated the bacillary bodies remaining after moderate extraction with ethyl alcohol as being an improvement of similar value over any of the others. Wilson had also made the important observation that the differences in the fixability of guinea pig complement, which Noguchi and Bronfenbrenner (4) had first called attention to in the case of the Wassermann reaction, were equally, if not more, important in the case of the fixation with tubercle materials. Our "standard" serum became exhausted and the work was set aside for the time being.

Later, another collection of human sera was classified and glycerinated. These became anticomplementary and remained so. It was evident that this method of obtaining a stable standard serum left us at the mercy of chance.

Four goats were now put in process of immunization, two with cultures of human type and two with a bovine type culture of low virulence

for guinea pigs and rabbits. One of the goats treated with the bovine culture never reached a fair titre and later died. The serum of the normal goat has an anticomplementary value of about 0.01 cc. The goats treated with human type cultures reached a fixation titre of 0.0001 at a maximum, but did not often reach or hold this value. It was not very satisfactory to work with them continuously because their fluctuations so often carried them near the dangerous anticomplementary zone. The second goat treated with the culture designated *Bovine 3* rather quickly reached a fixation titre of 0.0005, and it proved to be comparatively easy to keep it fluctuating between that point and 0.0001, which it reached as a maximum potency. No particular system of immunization was followed. The first dose given was 10 mgm. of the living culture. At first this was repeated at long intervals (six to eight weeks), and afterward more frequently. For some time temperature observations were made following the injections, and the dose was not repeated until the temperature had become normal. At first the temperature rise was prolonged, but later it lasted but two or three days, and still later but a few hours. Weight was not taken, but often there was evidently pronounced loss of weight and activity. Injections were not made at these times until it seemed that the animal was well on the up-grade. This animal has recently died, after having been under treatment at irregular intervals for over three years. Death was apparently caused by a superimposed infection. There were minimal evidences of chronic tuberculosis in the lungs and lymph nodes.

The serum of this animal, designated *S IV*, has been used as the basis for the work here reported upon, except where otherwise stated. The serum of titre 0.001, or better, may be mixed with glycerine, equal parts, for preservation. The anticomplementary value will increase with time, but not sufficiently to render the preparation unusable. If the serum is measured into test tubes, 0.1 cc. in each, these may be put in a vacuum dessicator over sulphuric acid and quickly dried. If the tubes are kept in the dessicator, the strength of the serum is maintained for years at least, and this makes a most satisfactory standard for comparison. Here the anticomplementary value does not sufficiently increase to bring it into consideration as a factor. The serum may be inactivated before being dried, but if it is potent this is unnecessary, and the serum heated before being dried redissolves with difficulty.

With this serum in hand as the basis for a further quantitative study we first went over certain of our earlier experiments, taking account of suggestions which had, in the meantime, been made by others. Wilson's observation on the variable quality of complement was confirmed and the recognition of it did much toward uniformity of result. We found that in one series of guinea pigs, eighty-six per cent gave good fixation, while eleven per cent gave slight fixation or none whatever. There were three per cent of the animals for whose complement the tubercle antigen alone was inhibitory. In other words, these behaved as though they might be infected with tuberculosis. They were killed, but a careful search failed to show evidence of disease. All work done after this was carried out with the complement of tested guinea pigs. In practice it has been found that these qualities are a lasting character of the animal.

Our earlier observations on the time factor in fixation had been done with the original Wassermann system so far as volume was concerned. The primary incubation was carried out in 1.5 cc., and this was increased to 3 cc. when the hemolytic reagents were added. The amount of blood cells was 0.5 cc. This was, of course, an expensive system as to reagents, and we now changed to the more modern one where the primary incubation is done in 1.0 cc. and the final volume about 1.2 cc., the amount of blood cells being 0.1 cc. of the usual 5 per cent suspension.

Petroff (5) had, in the meantime, taken cognizance of our point with regard to the time to be allowed for fixation and, while he recognized that the earlier practice of one-half or one hour was faulty, he found that for the conditions he was using our recommendation of four hours was unnecessarily long. He now proposed two hours as an adequate period. We therefore reëxamined this question. We found that, in fact, the reaction proceeds somewhat more rapidly with the system when the smaller volume is used regardless of the particular reagents (antigen) employed. This is in accordance with expectation, the reagents being actually present in greater concentration. Most of our earlier work had been done with bacillary emulsions as antigens. We now found that these are essentially slower in their action than Petroff's glycerine extract or than the alcoholic extract of which we speak at length later in this paper. Chart 1 is appended to show the conditions as we now understand them.

The reaction appears to be complete with the extractive antigens in two hours and with bacillary emulsion it is complete in three hours.

Even the shorter time now found for the emulsions may not be entirely due to the changed conditions of concentration (volume), since the readings are recorded at once after the completion of a half-hour second incubation. It is noted that if the tubes are stood in the icebox over night there is considerable additional hemolysis. This again is an indication that the reaction was not really quite complete. The four-hour period was originally fixed largely because of this very fact, that when it was used the readings changed very little on standing. However, from a practical point of view, the immediate reading is the

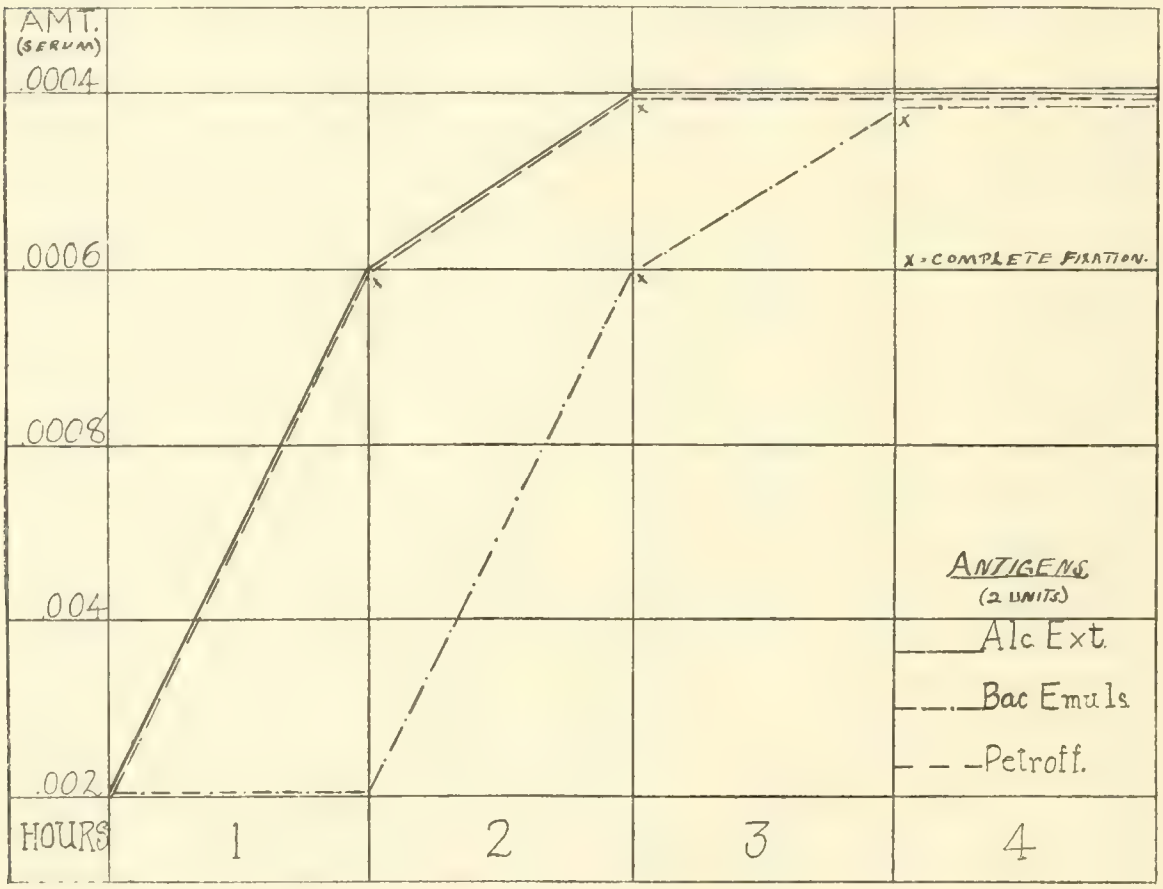

CHART 1

one which counts, and the two-hour primary incubation gives consistent results when reading is made at this time. This is doubtless a final opinion in so far as the extractive antigens are concerned. If, for any reason, one has occasion to do serious work with the bacillary suspensions, it would probably be advisable to reëxamine the time factor for them.

As had already been said, we had recognized a substance soluble in ethyl alcohol, as an important constituent of those antigens which we had tested for its presence. Wilson had proposed the use of the residue

remaining after the extraction of the bacillary bodies as an antigen. There seemed here to be the suggestion that we might have to do with a multiplicity of antigenic substances. We have, therefore, made some experiments to test this question. We placed a considerable quantity of the dried bacilli in a Soxhlet apparatus and subjected it to continuous extraction with ethyl alcohol. The alcohol was tested frequently for the presence of antigen, fresh alcohol being placed in the receiving flask on each occasion. The extraction was carried on until the alcohol, even when concentrated to less than one per cent of its volume, failed to show the presence of antigen. The extracted residue was then found to be without the slightest antigenic value. There is, then, no suggestion here of the presence of any but the one antigen. It is possible, of course, that some more labile substance may have been destroyed by the prolonged exposure to hot alcohol, but, granted that this possibility is present, it will take another method to demonstrate it, for a rough estimate of the quantity of antigen present in the alcohol showed that we had recovered far more active substance than it was possible to demonstrate in the bacilli employed as antigen in the unextracted condition.

Through these steps we had revised our technique, satisfied ourselves that the methods were adequate to give consistent results when applied with care, and, having a potent serum, stable and plentiful, we were able to proceed to the comparative study of the various questions which have been raised from time to time regarding the properties of the different antigenic preparations and the distribution of the antigenic principles. The results of this investigation are the chief subject of this paper.

The following method was uniformly used in determining the antigenic values: To 25 units of the immune serum there were added 2 units of guinea pig complement and varying amounts of the antigen under consideration. Normal salt solution was added to bring the total volume to 1.0 cc. After two hours' incubation in the water bath at 37.5°C., 4 units of antisheep amboceptor[2] and 0.1 cc. of 5 per cent sheep corpuscles were added. Each tube was then separately shaken and the tubes were returned to the bath for thirty minutes. The results were

[2] It will be noted that the hemolytic system contains an excess of amboceptor. In our earlier work a still greater excess (10 units) was used. This use of an excess of amboceptor is a fundamental feature of our experimental method. It is based on the conception that the union of antigen with antibody is slow in the case of tuberculosis and that it is in all probability more apt to be involved with various nonspecific factors than in the case of the lipoidal reaction with syphilitic materials. The

read immediately after removal. The least amount of antigen giving complete inhibition was taken as the criterion of activity. This amount (determined in the presence of an excess of the immune serum) we have called, for convenience, *one antigenic unit.*

It is conceivable that the units of antigens of different origin might not be truly equivalent. This would almost certainly be the case were the antigenic qualities of the various preparations due to different substances. This question has been tested by using 2 units each of the antigens as the basis for testing the titre of the immune serum. The serum was found to have the same value whichever antigen was used, provided the unit strength of the latter was respected, and provided the antigen originated from either human or bovine type of tubercle bacillus.

Tuberculin. A number of preparations of tuberculin were tested for their antigenic properties. Only the occasional one can be shown directly to possess any. This is because their anticomplementary value is usually very high. The additional point now made is that the result is not different when a serum of high potency is used from that obtained with the relatively weak human sera previously employed. It is to be presumed, from the fact that the active principle in tuberculin is precipitated by ethyl alcohol of any strength above 60 per cent, as was shown by Koch, and that the antigen we demonstrate with the fixation reaction is soluble in absolute alcohol, that the two substances are different. We have reinforced this presumption by giving intravenous injections of the alcoholic antigen in considerable quantity to goats in process of immunization. We have never been able to produce a rise of temperature although the animals were very sensitive.

Bacillary emulsion. When emulsions or suspensions of the tubercle bacillus are prepared with moderate attention to securing uniform content of the bacterial substance, they give indistinguishable results as antigens. This applies to the human and bovine types without regard to their period of isolation (whether recent or old) or to their virulence. For the bovine and human types the antigenic unit is about 0.1 mgm. The avian tubercle bacillus, on the contrary, is distinctly weaker than

amboceptor excess is presumed to disassociate these nonspecific factors and all except the most firmly bound portions of the complement attached to the specific complex, leaving in evidence only the fully completed portion of the specific reaction. Failure to recognize this technical feature (leaving the theoretical considerations quite aside) may easily account for the fact that some have had difficulty with crossed reactions when "Wassermann positive" sera were used with alcoholic extracts of the tubercle bacillus as antigens.

this; weaker also is a culture derived from a case treated a number of years ago with Friedmann's preparation (for this culture we are indebted to Dr. E. R. Baldwin of Saranac Lake). A culture, unpigmented, for which we are indebted to Dr. Duval and considered by him to have etiological significance in leprosy, also gives a low fixation value with this serum, as does a transplant of Kedrowsky's *Lepra* culture, likewise given us by Dr. Duval. The so called "yellow lepra" bacillus of Clegg and Duval gives no fixation whatever, nor do any of the other saprophytic acid-fast cultures which we have been able to study.

There is a suggestion here that the subject of specificity in this bacterial group may yet be approached with profit by serological methods.

Extracts of the tubercle bacillus. A fairly satisfactory antigen can be prepared by boiling a suspension of the tubercle bacillus in normal salt solution for fifteen minutes. Boiling for a shorter time, or heating for an hour to 50°, 60°, or 70°C. did not yield so potent an extract. Except to recognize the possibility of making a preparation in this way, which would give the same serum titre as other antigens, we have made no use of the method.

The glycerine extract of Petroff is one of the easiest preparations to make and to manipulate. Moulds may grow in it if it is not cared for, but this is its only drawback. The preparation by the method originally described was unnecessarily complicated. It is not, in fact, essential to spend any time in grinding the bacilli. If they are roughly emulsified in the glycerine water by a few minutes' trituration in a mortar, the boiled preparation, centrifugated to remove the larger particles, will be no less potent than the original, according to our experience.

The ethyl alcohol extract, to which we have referred in an earlier paragraph, requires but little further comment. The antigen is certainly by no means in a pure state in the alcohol. The first few hours' extraction, for example, brings out a substance which is strongly hemolytic. This hemolysin is not neutralized by the immune serum with which we have been dealing. Its real nature is unknown to us, and its only present interest is an indication that the alcohol doubtless extracts many substances other than the fixation antigen. The latter, it should be noted, is much more soluble in hot than in cold alcohol. It is also more soluble in hot alcohol than are other substances which are carried into the extract. When the extraction has proceeded for some time, the receiving flask accumulates a precipitate in increasing amount. This it is well to filter off at some convenient time, being careful to filter the

fluid hot. Then, when the filtrate cools, another flocculent precipitate will form. If this is also filtered off, much of the antigen will be removed with it. This flocculent matter redissolves immediately on bringing the fluid in which it is suspended to the boiling point. In practice, when the antigen is to be used, the stock flask is heated to boiling, and before it has had a chance to cool the required amount is removed and at once mixed with the required amount of salt solution in a test tube or small flask. The amount and the final dilution are naturally to be determined by experience, but once known they can be adhered to. Our usual preparations have been used in a dilution of 0.4 cc. of the alcoholic solution to 10.0 cc. of salt solution. The resulting fluid is at first very slightly opalescent. Over a period of hours this deepens to a cloudiness, followed by turbidity and finally by a definite precipitation. The antigenic value is maintained unchanged for hours, but disappears by the time the precipitate is formed. We have been content to work with suspensions within a few hours of the time they were made up, without following the fate of the antigen through the phases of its disappearance.

Further attempts to purify this antigen, fractionating it with ether and with acetone, have given somewhat conflicting results and have led to no improvement.

A preliminary study has been made of the comparative extractive potentiality for this antigen of a number of lipoidal solvents. The extraction was done in the Soxhlet apparatus and was continued for two days. At the end of this time the residue and the extract were tested for their content in antigen. The extract was dried at low temperature with a fan and redissolved in alcohol, as a preparation for the test. The bacillary residue was suspended in salt solution and tested in comparison with a suspension of similar weight made with unextracted bacillary bodies. The ligroin, toluene, and carbon disulphide extracts contained minimal quantities of the antigen; the ether and xylene contained slightly more; the carbon tetrachloride, chloroform, acetone, benzol, normal butyl alcohol and ethyl alcohol were all equally strong. The residue had been most weakened by carbon tetrachloride and least by chloroform, among those solvents which had extracted considerable quantities of the antigen. The extraction was evidently too short to lend particular significance to the result. Considering the fact above cited, that boiling normal salt solution extracts more than merely demonstrable quantities of the substance and the wide range of the organic

solvents which are more or less effective as extractives, it is evident that any thought of characterizing this antigen on the basis of its solubility relationships must be set aside until a more exhaustive study of the subject has been made.

Body fluid and tissues of tuberculous animals. It has frequently been maintained by others that tubercle antigens could be demonstrated in the tissues and body fluids of infected human beings or animals. We have not studied this question exhaustively. We have, however, tried to see whether, with the use of a potent serum for the test, the alcohol solubility of the antigen might make possible an easy demonstration. The attempt was a complete failure. The alcoholic extract of tuberculous guinea pig spleen is hemolytic; that of the liver is strongly anticomplementary. It may be that these conditions mask the antigen, but in any event we did not succeed in demonstrating the latter. Similarly, we failed to show the presence of any antigenic substance in the alcoholic extract of the dried blood serum or the dried urine of patients with advanced tuberculosis. Separating the acetone-insoluble fraction of the alcoholic extract did not lead to any better result. The milk of a ewe under immunization, receiving large quantities of tubercle bacilli intravenously during the period examined, failed to show the antigen. The milk did contain the complement-fixing antibody.

Clinical application. We have made a study of the alcoholic antigen as compared with a suspension of the living human type tubercle bacillus and Besredka's antigen, using a series of human sera. The result appears in the following table. Allowing for the fact that the bacillary suspensions would be a little low because of the two rather than the three or four-hour primary fixation period, it seems clear that there are no great differences between the antigens.

	ALCOHOLIC EXTRACT		BESREDKA'S ANTIGEN		BACILLARY EMULSION	
	Number	Per cent	Number	Per cent	Number	Per cent
Positive	46	27.8	48	29.1	38	23.1
Negative	119	72.2	117	70.9	127	76.9
Total	165		165		165	

In a less systematic way, Petroff's glycerine extract antigen has frequently been compared with the alcoholic extract and has always given about the same result.

DISCUSSION AND SUMMARY

Our study as here reported seems to justify the conclusion that in the recent past those who have worked with complement fixation in tuberculosis have given undue weight to the antigen and have paid too little attention to other fundamental factors concerned in the reaction.

We find no evidence of more than one antigenic substance, and this is found in acceptable form in several preparations. Petroff's glycerine extract, Besredka's antigen, the alcoholic extract of the tubercle bacillus used by Craig, the simple suspension of the living tubercle bacillus and doubtless the "autolysate" of Corper are of essentially equal worth. The alcoholic extract and the glycerine extract are the easiest to prepare and keep, the alcoholic extract being superior in the latter respect.

The most important feature of the reaction is that the time of primary incubation is longer than in the classical Wassermann reaction (two to four hours, as against one-half hour). The longer time is necessary to secure comparable results with the bacillary suspension which becomes less practical on this account, as well as by reason of its limited keeping qualities.

While the evidence is not presented here, our experience has continued to show that the application of the reaction in practice is limited by the fact that about ten per cent of the clinically normal persons give a positive reaction. This is not materially different with any antigen.

We have been fortunate in developing an immune goat serum with high potency in the fixation reaction, and with this as a starting point,—a tentative standard,—have assured ourselves that under suitable conditions the reaction is a constant and reliable one.

We have failed to demonstrate antigenic substances in the body fluids and tissues of tuberculous animals by extraction with alcohol.

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A SIMPLE LABORATORY GAS METER AND AN IMPROVED HALDANE GAS ANALYSIS APPARATUS.

By H. S. NEWCOMER.

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Carpenter (1) has described in detail the methods which are available for the study of respiratory exchange in man. Of these the simplest is that of Douglas which depends upon the collection of a specimen of expired air in a rubber bag and the determination of its CO_2 and O_2 percentages in a Haldane gas analysis apparatus (2). Since the publication of Carpenter's work, several types of apparatus have appeared. They all determine the calorie production by methods of measuring the reduction in the oxygen volume in a closed system which includes the patient's respiratory tract. The methods, while simple, are not always satisfactory. In so far as they are limited to the determination of oxygen consumption, they fail to give as much information as is frequently desired concerning the gaseous metabolism. This paper describes some improvements in apparatus to be used in connection with methods similar to those of Douglas.

For the collection of expired air, one may use in addition to a suitable face mask and valves, either a calibrated spirometer (3) or a properly constructed rubber bag. A spirometer is less portable and more expensive. The rubber bag designed by Douglas furnishes an easy and portable means of collecting the expired air. For the measurement of the volume of its contents, it is customary to use a wet meter of the Bohr type. The Danish meters are very expensive, but those made in this country, while less elegant, are very reliable. They maintain vapor saturation of the expired air but there is no data available as to the error which they introduce by the absorption of the CO_2 from the air

passed. They are not very portable and to read correctly must have the water level closely adjusted. In the case of the $\frac{1}{10}$ cubic foot size, the volume read is 1 per cent low for each $\frac{1}{16}$ inch rise of the water level above the mark set. The meters have a slow rate of flow and if the rate be more than about $\frac{1}{3}$ cubic foot per minute there results a rise in the water level producing a contrac-

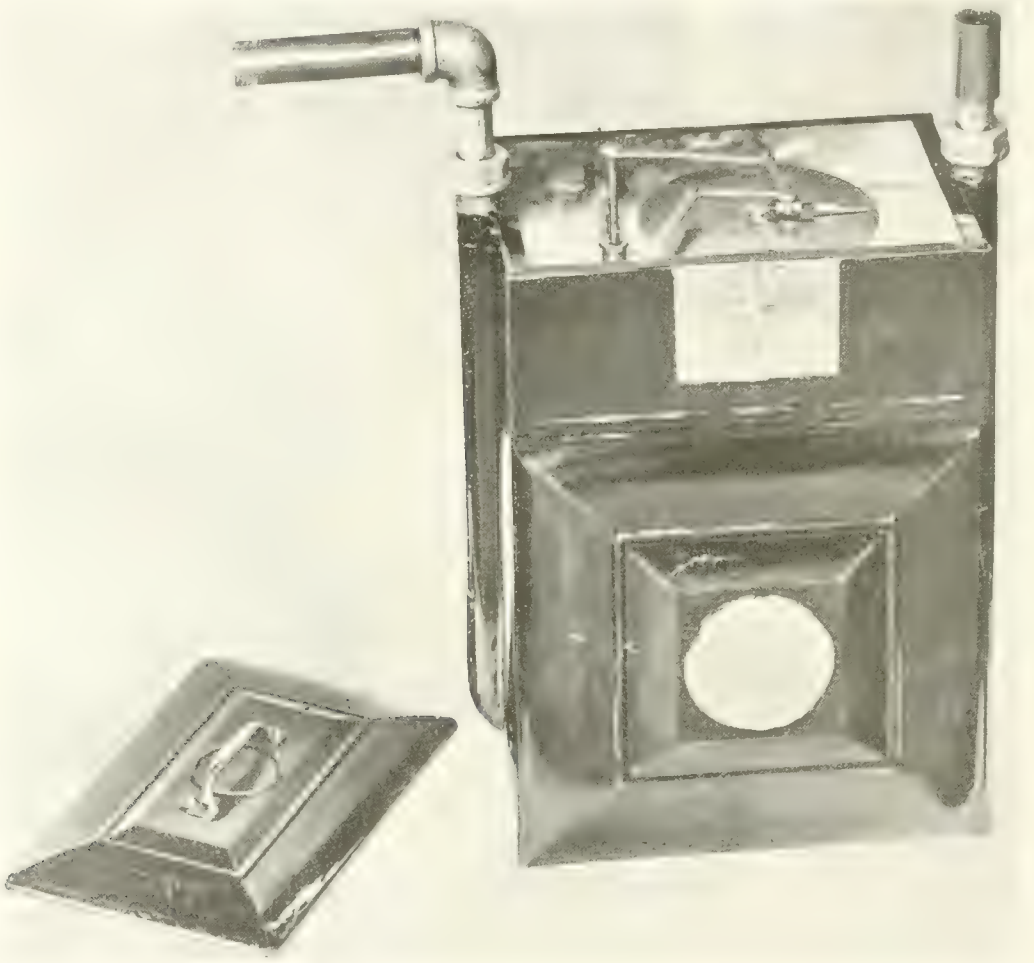

Fig. 1.

tion in the volume reading which may readily amount to 4 per cent. It is easy by increasing the rate, to cause the air to bubble through the meter and increase this error to 20 per cent or more.

An inexpensive and portable meter may be adapted from the ordinary five light gas service meter (Fig. 1). This meter has two soft oiled leather bellows in closed compartments, and works as a tandem reciprocating engine to rotate a vertical shaft at the

rate of one revolution per $\frac{1}{8}$ cubic foot of gas passed. A worm drive from this operates the dial. The top of the meter may be removed, or the meter purchased without a top, and a graduated circle and hand placed on the vertical shaft. It then reads about 3,540 cc. per revolution. The factory adjustment of the meter is made to within about 1.0 per cent of this figure. The meter may be calibrated by displacing air from a large bottle with tap water.

The calibration of two such meters was done by delivering air from a 10 cubic foot standard meter prover of the spirometer type in one of the laboratories of the United Gas Improvement Company. The air was delivered under pressures varying from 0.5 to to 2.5 mm. of Hg. The speed varied from 2 to 4 cubic feet a minute. A test performed with a standard cubic foot bottle, correct to one part in ten thousand and delivering air much slower, gave the same readings as the slowest of the above speeds. During numerous consecutive runs the variation in the meter reading was at any one pressure never more than two parts in one thousand. There was a variation due to pressure changes. Up to a speed of 2 cubic feet per minute the readings were constant. At 3 cubic feet per minute (1.6 mm. of Hg) the reading for 10 cubic feet (corrected) was 0.6 per cent low and at 4 cubic feet per minute (2.5 mm. of Hg) the reading was 1.0 per cent low. When calibrated at low speeds and used at higher speeds the meter reading can therefore be increased in these proportions. The decreased readings at higher pressures do not seem to be due to leakage through the reciprocating valves of the meter.

If the zero of the dial on the main shaft be taken as the top with the meter facing the operator, then Fig. 2 represents the calibration curves of two of these meters when run in series with a Bohr meter. The hand does not run evenly around the circle but varies by as much as 180 cc. from the expected value. The correction curves for the two instruments are about alike and the unevenness is a part of the design of the apparatus. A calibration curve of this form will correct for this error and such a correction may be applied in case the meter is used under conditions in which such a difference is of importance. For metabolism experiments in which the total volume is large compared with 180 cc., this error may be neglected. It is of about the order of magnitude of the error in reading the position of a spirometer bell.

The expired air is saturated with water vapor and is at a relatively high temperature. If it is, however, allowed to cool before being measured care must be taken that the meter is not warmer than the air for in passing through it will be warmed and no longer be vapor-saturated. To obviate this, on admitting the air to the meter, it may be passed through a water bottle slightly warmer than the meter. The temperature of the air whose volume is measured by the meter had best be taken by hanging a thermometer in the exit tube. The thermometer should reach its end-point quickly.

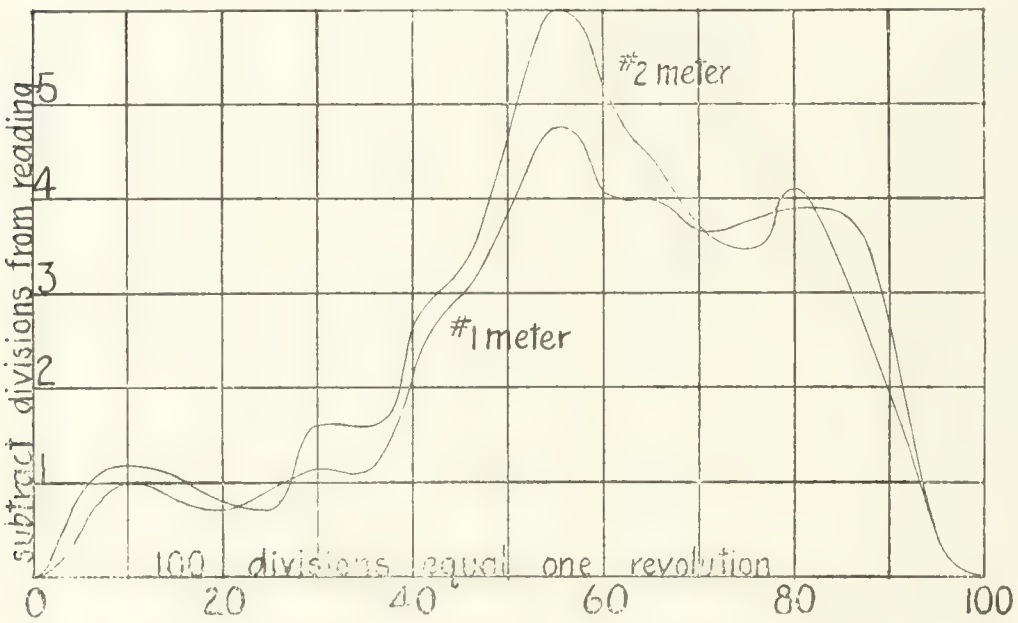

Fig. 2.

For the analysis of the expired air it is customary to use the portable gas analysis apparatus devised by Haldane (Fig. 3). The construction of this, as it is ordinarily obtained, is crude. It may be much improved by constructing a more adequate rack for the mercury leveling bulb and adding a similar one for the potash bulb. The various parts are usually connected by pieces of rubber tubing. These dry out and in any event are subject to leaks which are always suspected as possible sources of error. The principal glass parts may be blown in one piece so that there is only connecting rubber tubing below liquid levels. It is advisable to place a mercury trap between the burette and potash bulb, a feature which frequently saves much time. An additional improve-

ment is to place all the glass parts in a water bath instead of only the burette and its control. The apparatus is then less sensitive to currents of air producing temperature changes. Since it may be desirable to fill the gas burette to exactly 10 cc., it is necessary

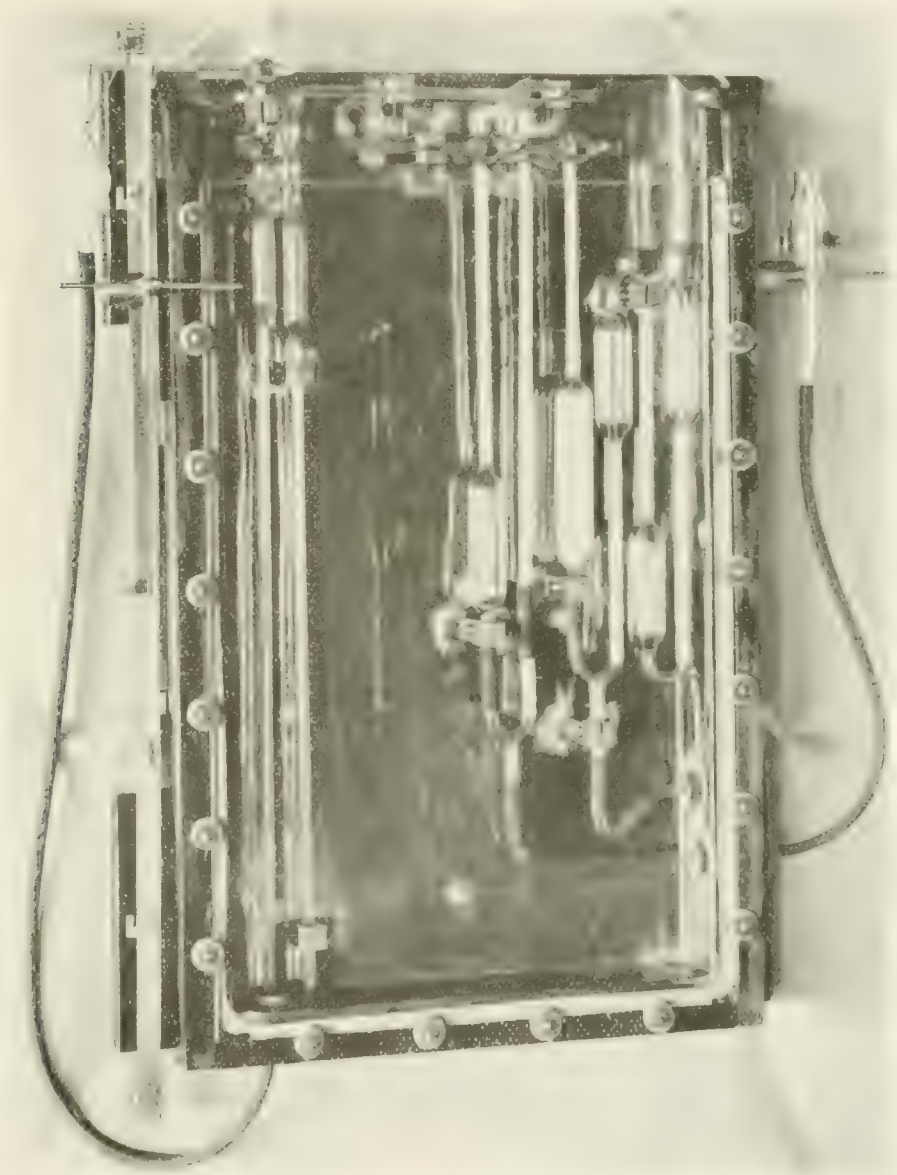

Fig. 3.

to have several graduations on the potash burette, about five at millimeter intervals, one of which may serve as an initial reading. The water bath may be constructed of a copper-lined box faced in front with plate glass, using rubber tubing as a washer between

the copper flange and the glass. The two racks and pinions may then be placed one at each side of the instrument and the connections to the leveling bulbs brought out through corks inserted in thimbles in the walls of the bath. These rather simple improvements do much to make the apparatus easier to work with.[1]

SUMMARY.

There is described a simple, accurate, and relatively inexpensive laboratory gas meter, being an adaptation of the common five light service meter.

Some improvements in the Haldane gas analysis apparatus are described.

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[1] The meter with dials attached and the modified Haldane apparatus may be obtained from the Arthur H. Thomas Co., Philadelphia.

AIDS TO BASAL METABOLIC RATE DETERMINATIONS *

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This paper contains charts and tables so arranged as to facilitate considerably the otherwise laborious calculation of basal metabolism values. They are in such form as to be useful in calculating basal metabolic rate from data obtained with any form of apparatus. They are intended primarily for use in connection with determinations made by some method involving the use of a Haldane gas analysis apparatus. Such methods in common use are either that described by Boothby and Sandiford [1] in which the expired air is collected in a large spirometer, or the method of Douglas [2] in which a rubber bag is used for this purpose and the volume of its contents measured with a meter.[3] In either of these methods the gasometric data include figures for volume, temperature, pressure, and carbon dioxid and oxygen content of the expired air. From these are to be computed the respiratory quotient and oxygen consumption at standard conditions of temperature and pressure. The figure for oxygen consumption, when multiplied by the calorific value of oxygen, gives a figure for calory production.

Certain instruments, as for instance the Benedict portable apparatus,[4] read the uncorrected oxygen consumption directly and a respiratory quotient of 0.82 corresponding to a calory value per liter for oxygen of 4.825 is assumed.

In calculating basal metabolic rate, the patient's calory production is compared with the normal. It is generally customary to use as standards the figures of Aub and DuBois, giving the normal calory production per square meter of body surface. The body surface of the patient is calculated from the height weight chart of DuBois. There are also available the standard multiple prediction tables of

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* From the Laboratory of the Henry Phipps Institute of the University of Pennsylvania.

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Benedict, as well as certain other data, applying to children.[5] In its simplest form the calculation is laborious and when it is desirable to obtain the additional information to be had by the use of a Haldane apparatus, the computation involves the expenditure of an appreciable amount of time and gives opportunity for the appearance of numerical errors.

The use of the charts and tables at the end of this paper restrict this labor to the performance of a simple algebraic sum. In several instances they condense hitherto available tables of many pages to a single sheet. There follows a description of their derivation and then directions for their use with examples.

Derivation of Formulae and Charts.—Charts 1 and 2 are intended for use with the Haldane gas analysis apparatus and are used to obtain hourly calory production. Chart 2 corrects the gas volume to standard conditions of temperature and pressure and includes a correction for water vapor.

Apparatus such as that of Benedict which reads oxygen consumption directly, that is, which reads the diminution in oxygen volume of a closed system including the patient's respiratory tract, does not involve a correction for water vapor. The observed diminution in oxygen volume is, therefore, to be reduced to standard conditions by a factor which does not include a correction for saturation with water vapor. Chart 3 supplies the logarithm of this correcting factor. The hourly calory production may be obtained by multiplying the oxygen consumption in c.c. per minute by 0.2895 (log. $0.2895 = \overline{1}.4617$). The other charts and tables have to do with basal metabolism standards. In the computation of the charts and tables five figure logarithms were used except that in the case of Chart 1 it was necessary to use seven place tables.

Chart 1 has as abscissae the reading of the Haldane buret after absorption of carbon dioxid, it being assumed that the Haldane buret was filled in the first place to the 10 c.c. mark at atmospheric pressure. The ordinates are the Haldane readings after carbon dioxid and oxygen absorption. It is further assumed that these readings are corrected for any calibration error which the Haldane buret may have, and that the patient breathes outside air. This may be either through a tube out the window, or, if the room can be well aired, it suffices to leave the window open for some time before starting. The chart has two families of lines; the horizontal ones give, by interpolation between them, the value of the respiratory quotient, volume of carbon dioxid production divided by volume of oxygen absorption. The more vertical lines are the logarithms of factors, portion of oxygen absorbed times the calorific value of one liter of oxygen at the equivalent respiratory quotient. The value of the logarithm of this factor corresponding to any pair of Haldane readings is obtained by interpolation between this family of lines.

5. Carpenter, T. M.: Carnegie Inst. Wash. Pub. No. 303, 1921.

TABLE 1.—Barometer Correction for Change in the Value of Gravity with Latitude to Be Subtracted from or Added to the Observed Height of the Barometer Before Going to Charts 2 or 3

Latitude	0° 90°	5° 85°	10° 80°	15° 75°	20° 70°	25° 65°	30° 60°	35° 55°	40° 50°	45° 45°
710 mm. Subtract mm. Add	1.84	1.81	1.73	1.59	1.41	1.18	0.92	0.63	0.32	0.00
760 mm. Subtract mm. Add	1.97	1.94	1.85	1.70	1.51	1.27	0.98	0.67	0.34	0.00

The correction varies with the height of the barometer. To correct for altitude subtract 0.14 mm. of mercury for every one thousand meters above sea level. To correct for the capillary depression of the mercury column see the text. Combine all of these corrections into one and use only if significant.

TABLE 2.—Logarithms of Standard Reciprocal Normal Basal Metabolism Factors for Children 17 Years of Age and Under Referred to Weight in Pounds. (Benedict)

Wt.	Boys	Girls	Wt.	Boys	Girls	Wt.	Boys	Girls	Wt.	Boys	Girls
6	$\overline{1}$.264	$\overline{1}$.274	36	$\overline{2}$.498	$\overline{2}$.523	66	$\overline{2}$.333	$\overline{2}$.360	96	$\overline{2}$.270*	$\overline{2}$.288
8	.106	.093	38	.485	.510	68	.326	.351	98		.287
10	$\overline{2}$.996	$\overline{2}$.974	40	.472	.498	70	.318	.344	100		.286
12	.908	.885	42	.455	.487	72	.311	.337	102		.285
14	.835	.813	44	.444	.475	74	.304		104		.284
16	.774	.758	46	.433	.463	76	.297	.320*	106		.283
18	.724	.712	48	.422	.451	78	.291		108		.282
20	.682	.679	50	.411	.440	80	.285	.305*	110		.281
22	.645	.649	52	.400	.430	82	.280		112		.280
24	.614	.621	54	.390	.419	84	.274	.295	114		.279
26	.589	.595	56	.379	.408	86		.294	116		.278
28	.567	.572	58	.368	.399	88		.292	118		.277
30	.547	.564	60	.358	.389	90		.291	120		.276
32	.529	.549	62	.350	.379	92		.290	124		.274
34	.513	.536	64	.342	.371	94		.289	128	.260*	.272

The figures are the logarithms of reciprocal total calories per hour of children weighing from 6 to 128 pounds. The figures are calculated from data by Benedict and Talbot, and Benedict and Hendry. The numbers with an asterisk are not due to these authors but are supplied as probable values in order to make the table complete

TABLE 3.—Three Figure Logarithms

	0	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9
1	000	041	079	114	146	176	204	230	255	279	4 3 3 3 2	8 7 6 6 5	12 10 9 8 7	16 13 12 11 10	20 17 15 13 12	24 20 18 16 14	28 24 21 18 16	32 27 24 21 19	36 30 26 23 21
2	301	322	342	362	380	398	415	431	447	462	2 2 2	4 4 3	6 5 5	8 7 6	10 9 8	12 11 9	14 12 11	16 14 12	18 16 14
3	477	491	505	518	531	544	556	568	580	591	2 1	3 2	4 4	6 5	7 6	8 7	10 8	11 9	12 10
4	602	613	623	633	643	653	663	672	681	690	1	2	3	4	5	6	7	8	9
5	699	708	716	724	732	740	748	756	763	771	1	2	2	3	4	5	6	6	7
6	778	785	792	799	806	813	820	826	833	839	1	1	2	3	3	4	5	5	6
7	845	851	857	863	869	875	881	886	892	898	1	1	2	2	3	4	4	5	5
8	903	908	914	919	924	929	934	939	944	949	1	1	2	2	3	3	4	4	5
9	954	959	964	968	973	978	982	987	991	996	1	1	1	2	2	3	3	4	4
	0	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9

The figures of the table are the mantissae of two figure numbers. The columns at the right are the proportional parts to be added to the mantissae to make them the mantissae of three figure numbers. The characteristic of the lograrithm is the number less one of integral digits in the number.

TABLE 4.—Three Figure Antilogarithms

	0	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9
0	100	102	105	107	110	112	115	117	120	123	0	1	1	1	1	2	2	2	2
.1	126	129	132	135	138	141	145	148	151	155	0	1	1	1	2	2	2	3	3
.2	158	162	166	170	174	178	182	186	191	195	0	1	1	2	2	2	3	3	4
.3	199	204	209	214	219	224	228	234	240	245	1	1	2	2	3	3	4	4	5
.4	251	257	263	269	275	282	288	295	302	309	1	1	2	3	3	4	5	5	6
.5	316	324	331	339	347	355	363	371	380	389	1 1	2 2	2 3	3 4	4 4	5 5	5 6	6 7	7 8
.6	398	407	417	427	437	447	457	468	479	490	1 1	2 2	3 3	4 4	5 5	6 7	7 8	8 9	9 10
.7	501	513	525	537	550	562	575	589	603	617	1 1	2 3	4 4	5 5	6 7	7 8	8 10	10 11	11 12
.8	631	646	661	676	692	708	724	741	759	776	1 1 2	3 3 4	4 4 5	6 6 7	7 8 9	9 10 11	10 11 12	12 13 14	13 14 16
.9	794	813	832	851	871	891	912	933	955	977	2 2 2 2	4 4 4 5	6 6 6 7	8 8 8 9	9 10 11 11	11 12 13 13	13 14 15 16	15 16 17 18	17 18 19 20
	0	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9

The figures of the table are the numbers corresponding to two figure mantissae. The columns at the right are proportional parts to be added to the numbers to make them numbers corresponding to three figure mantissae. The characteristic of the logarithm is omitted in going to the table. The number is to be pointed off so as to have a number of integral digits equal to the characteristic plus one. If the characteristic is negative the number is to be prefaced by a number of decimal zeros equal to the characteristic plus one (with regard to sign).

The derivation of these two families of lines is as follows:

Let x=reading of Haldane after CO_2 absorption
=100—CO_2 percentage in expired air
y=reading of Haldane after $CO_2 + O_2$ absorption
(1) =100—($CO_2 + O_2$) percentage in expired air
=nitrogen percentage in expired air

If 20.93 be the value taken for the oxygen percentage in the inspired air, outside air, and 0.03 the carbon dioxid percentage, then 79.04 is the nitrogen and other inert gas percentage in the inspired air. The fraction $\frac{y}{79.04}$ represents the change in volume of the air due to alveolar gas exchange, and the oxygen absorption in per cent. is given by

$$(2) \qquad \frac{20.93\,y}{79.04} - O_2 = K$$

where O_2 is the oxygen percentage of the expired air. From (1) and (2)

$$\frac{20.93\,y}{79.04} + y - 100 + CO_2 = K$$

or

$$(3) \qquad \frac{99.97}{79.04}\,y - x = K$$

These are a family of lines of slope $\frac{79.04}{99.97} = .790637$ giving constant oxygen absorption K. The values of the calorific equivalent, C, of one liter of oxygen for the respiratory quotients 0.707 to 1.00 as tabulated by Lusk[6] are given with an error of less than one part in one thousand by the formula

$$R.\ Q. = 0.813\ C - 3.103$$

But by definition $R.\ Q. = \frac{100-x-0.03}{K}$

Therefore

$$\frac{100-x-0.03}{K} = 0.813\,C - 3.103$$

$$C = \frac{100-x-0.03}{0.813K} + \frac{3.103}{0.813}$$

$$(4) \qquad CK = \frac{100-x-0.03}{0.813} + \frac{3.103}{0.813}\,K$$

substituting (3) in (4)

$$CK = \frac{100-x-0.03}{0.813} + \frac{3.103}{0.813}\left(\frac{99.97}{79.04}y - x\right)$$

$$CK = 4.8274y - 5.04674x + 122.9643$$

= per cent. oxygen absorbed times its calorific value per liter.

This family of lines is plotted for values of CK whose logarithms are 0.60, 0.65, 0.70, etc., to 1.55. K is the number representing per cent. oxygen absorbed by the patient. The fraction $\frac{K}{100}$ is, therefore, a number which multiplied by the expired volume is the oxygen absorbed by the patient. $\frac{CK}{100}$ is its calorific value and the logarithms of $\frac{CK}{100}$ instead of the above logarithms of CK are assigned as signatures to the family of lines, namely, $\bar{2}.60$, $\bar{2}.65$, $\bar{2}.70$, ... to $\bar{1}.55$.

6. Lusk, G.: The Science of Nutrition, Ed. 3, Philadelphia, 1919, p. 61.

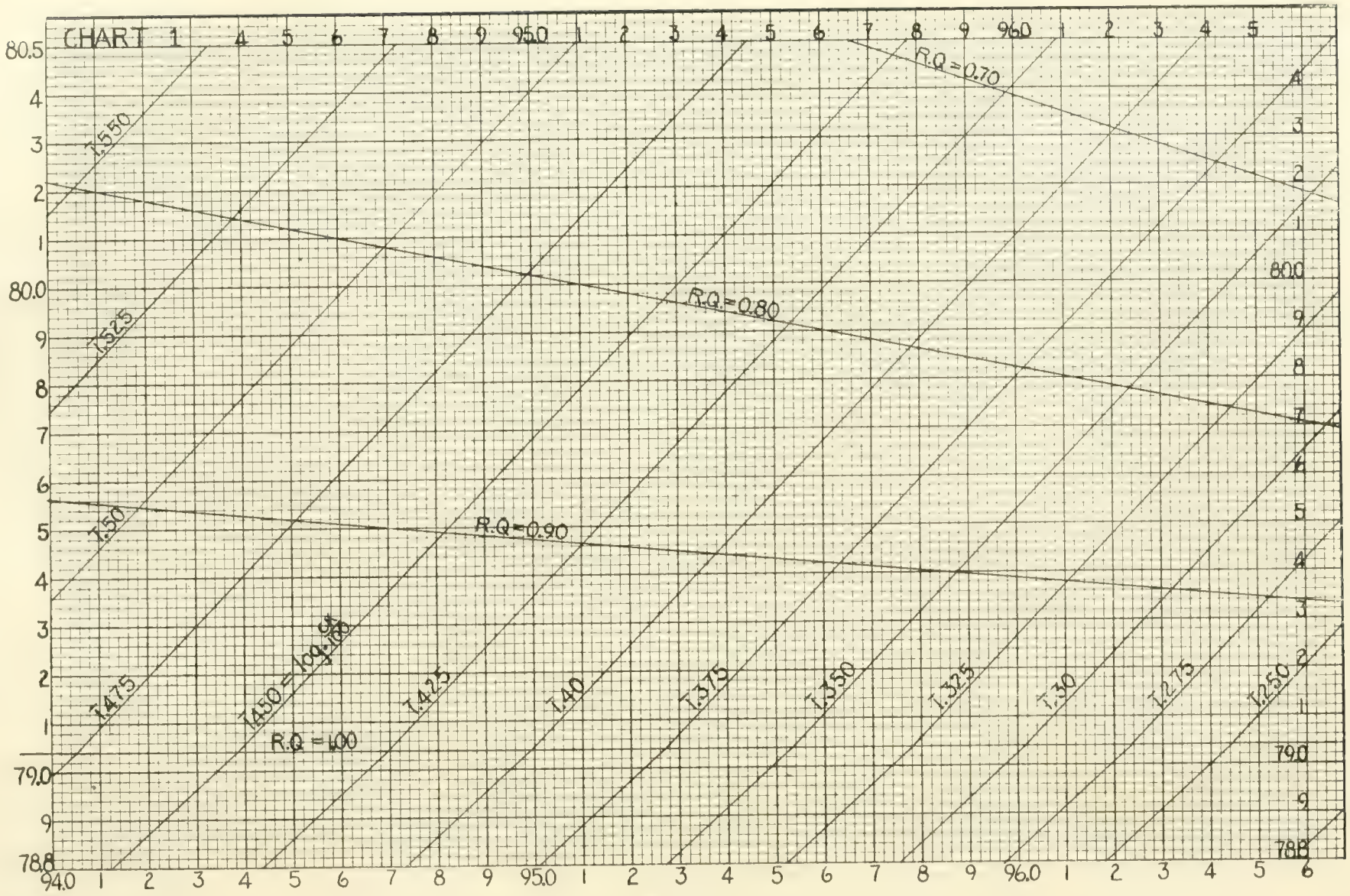
CHART 1
R.Q.=0.70
R.Q.=0.80
R.Q.=0.90
R.Q.=1.00
1.550
1.525
1.50
1.475
1.450=109.9%
1.425
1.40
1.375
1.350
1.325
1.30
1.275
1.250

Chart 1A.

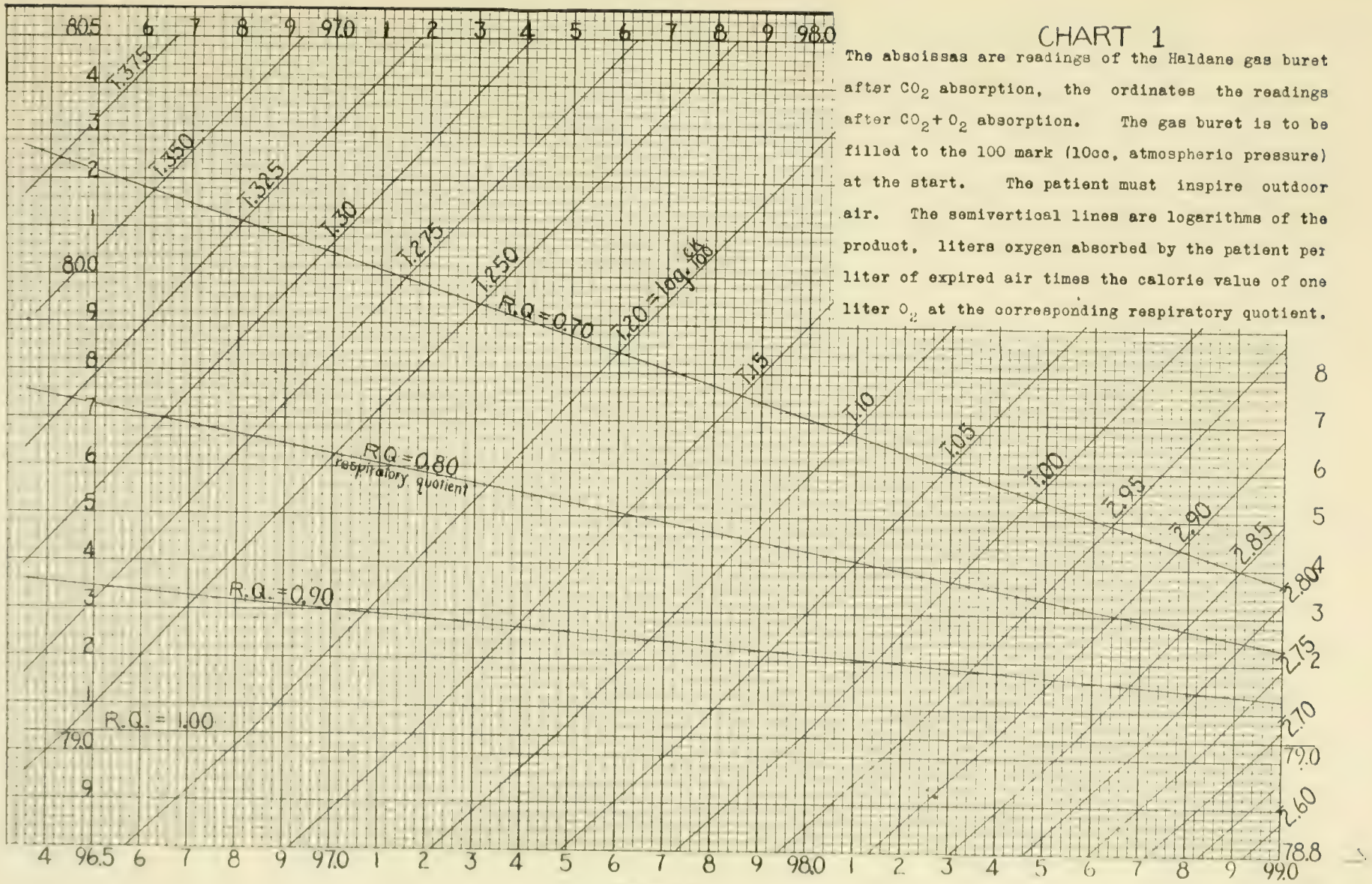

Chart 1B.

CHART 1

The abscissas are readings of the Haldane gas buret after CO_2 absorption, the ordinates the readings after $CO_2 + O_2$ absorption. The gas buret is to be filled to the 100 mark (10cc. atmospheric pressure) at the start. The patient must inspire outdoor air. The semivertical lines are logarithms of the product, liters oxygen absorbed by the patient per liter of expired air times the calorie value of one liter O_2 at the corresponding respiratory quotient.

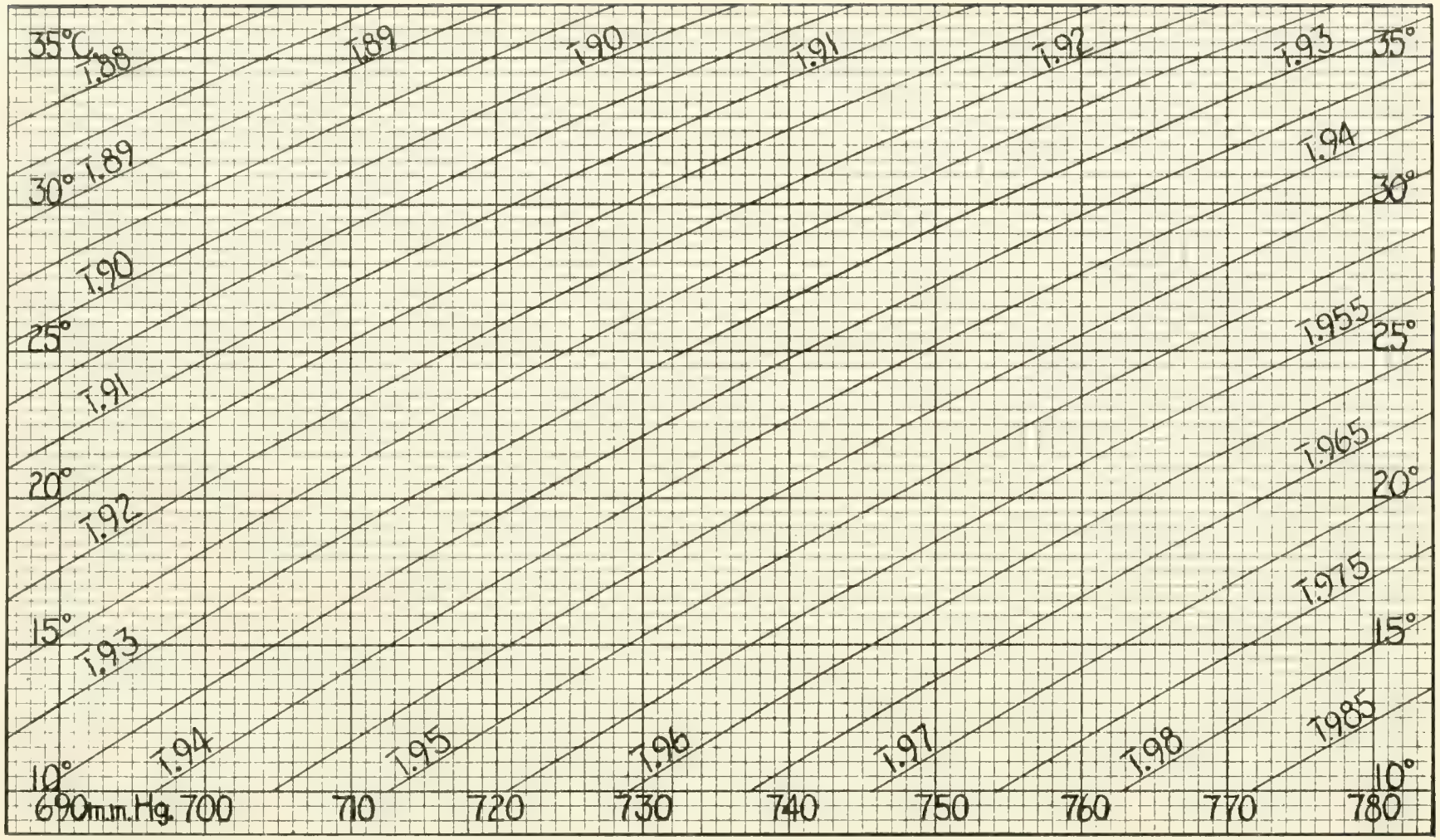

Chart 2.—The ordinates are temperatures centigrade and the abscissas observed barometric pressures in mm. of mercury. The lines are logarithms of the factor reducing observed volume of water vapor saturated air to 0 C., dry, 760 mm. sea level and latitude 45 degrees, including a reduction of the barometer readings, brass scale, to 0. C. Log $\frac{\text{p — vap. ten. — scale correction}}{760} \times \frac{1}{1+0.00367\ t}$

For the other corrections which may be advisable see Table 1.

When the respiratory quotient is greater than unity the heat production is due to the oxygen consumption plus the heat produced in the transformation of the carbohydrate into fat during which the extra carbon dioxid was produced. The heat value of this transformation, according to Lusk, is 0.8 calories per liter carbon dioxid. For readings below the line RQ = 1 carbohydrate is being burned at a rate producing an oxygen percentage absorption corresponding to a CK line of the reading where C is the 5.047 of RQ = 1. In addition, carbohydrate is being converted into fat with a carbon dioxid percentage production equal to the difference between x where the CK line crosses RQ = 1, and the observed x. To this additional CO_2 there corresponds a calory production of 0.8 per liter. In order to calculate the total calory factor, we may draw a line of the family K = constant through the point given by the intersection of the CK line and RQ = 1. If this be considered as a new CK line it is a line along which neither C nor K changes. The new calory factor line is then one passing through the CK, RQ point and having a slope sufficiently steeper than the constant K line to make an observed point on the constant K line and one x unit smaller than the x of the CK, RQ point lie 0.8 of the distance between the new line and a next parallel one having a value one unit larger. Therefore, below the line RQ = 1, the constant calory factor lines bend slightly, as shown in the chart, and for readings below the line RQ = 1, the patient is putting on fat at the moment in question.

Chart 2 is computed from data by Kaye and Laby.[7] It is a family of curves giving by interpolation the logarithms of the factor reducing the observed air volume to 0 C., 760 mm. of mercury at latitude 45 degrees and sea level, dry, together with a correction to 0 C. of the mercury columns and brass scale. The corrections for brass and glass scales are nearly the same. At 10 C. the correction for glass to be subtracted is 0.07 mm., and at 34 C., 0.25 mm. greater than that correction for brass which has been subtracted from the barometric height in computing the curves. The table does not include barometer corrections due to the change in the value of gravity with latitude and height above sea level. If it is desired to correct for latitude, add or subtract from the observed barometer the figures of Table 1 before reading from the chart. The change in gravity due to altitude is such that for every one thousand meters above sea level one should subtract from the observed barometer approximately 0.14 mm. of mercury. It may be proper in addition to correct for the capillary depression of the mercury column. This correction is zero if both mercury levels have the same cross section, as is the case with the usual all glass barometer. For barometers having a mercury reservoir the figures to be added to the barometer reading for bores of 4, 5, 6, 7, and 8 mm. are, respectively, 1.2, 0.7, 0.4, 0.25, and 0.2 mm., provided the height of the meniscus itself is 0.6 mm. For heights of the meniscus greater than this and up to 1.6 mm. these figures are to be increased uniformly per 0.2 mm. of height respectively by 0.4, 0.25, 0.2, 0.15, and 0.1 mm. These corrections for gravity and capillary depression may of course be determined at any place once for all and combined into one single correction for the barometer.

Table 2 is derived from data by Bendict and Talbot[8] and Benedict and Hendry.[9] It gives the logarithms of the reciprocal of the total number of calories produced per hour by children seventeen years of age and under. The numbers are computed from the tables of these authors. The numbers with an asterisk are supplied to make the table complete, the two for girls being easily inserted by interpolation. The additional numbers for boys cannot be supplied with the same assurance. There should be a continued gradual decrease in the

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7. Kaye, G. W. C., and Laby, T. H.: Table of Physical and Chemical Constants, Ed. 2, London, 1916.

8. Benedict, F. G., and Talbot, F. B.: Carnegie Inst. Wash Pub. No. 302, 1921, p. 206.

9. Benedict, F. G., and Hendry, M. F.: Boston M. & S. J. **184**:329, 1921.

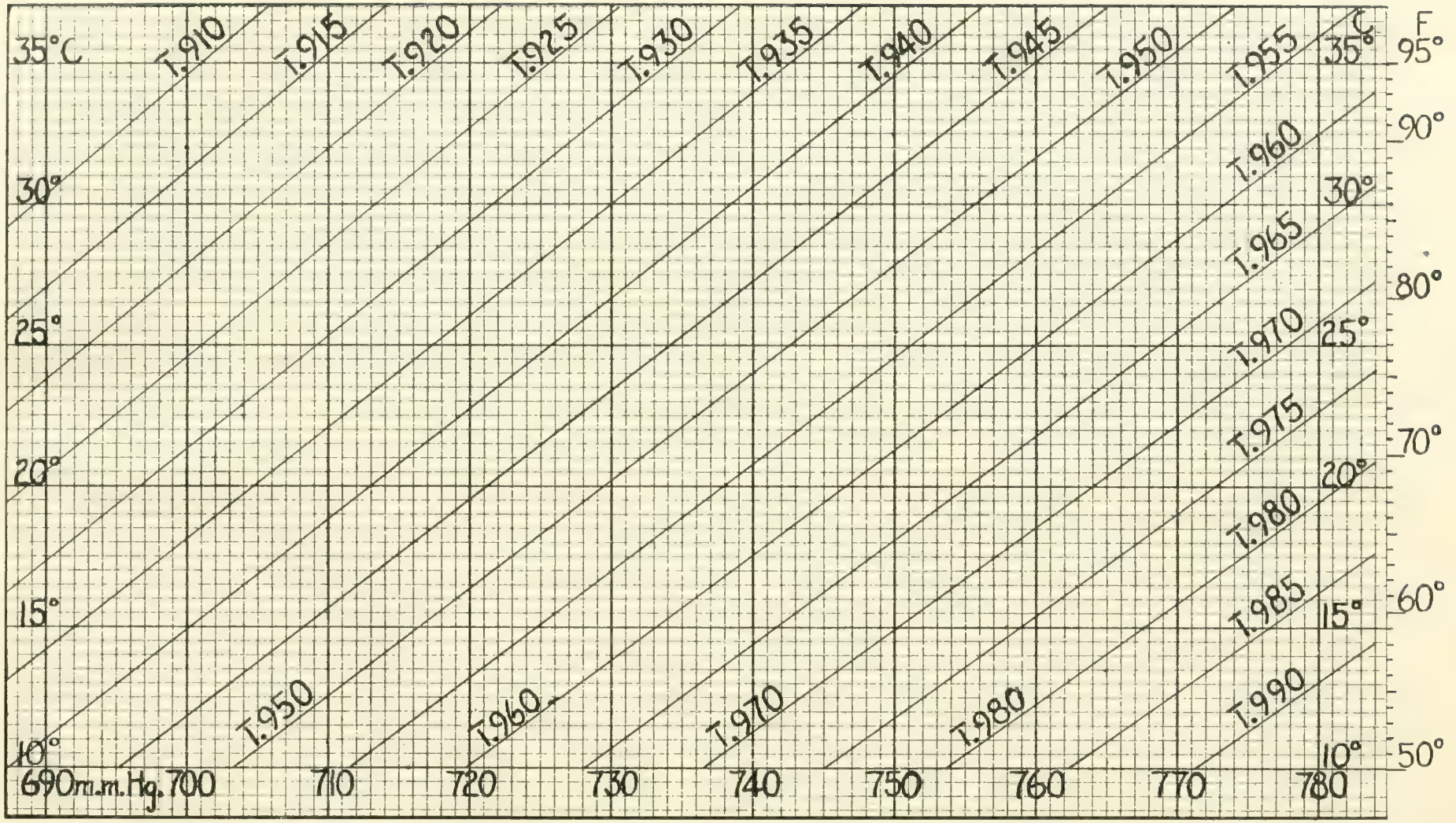

Chart 3.—The ordinates are temperatures centigrade and the abscissas observed barometric pressures in mm. of mercury. The lines are logarithms of the factor reducing observed volume of dry air to 0 C., 760 mm. sea level and latitude 45 degrees, including a reduction of the barometer readings, brass scale, to 0 C. Log $\frac{\text{p} - \text{scale correction}}{760} \times \frac{1}{1+0.00367\ \text{t}}$

For the other corrections which may be advisable see Table 1.

logarithms with increasing weight. The least decrease that could be expected is to the figure $\bar{2}.260$ at 128 pounds. A smaller figure could not well be chosen because of the fact that in adults of the age of twenty-one years, having the extreme range of weights and normal stature (Prudential 1912 statistics), the normal calory production for males (Benedict multiple prediction formula) is not more than 3 per cent. higher than that of females. The antilogarithms of $\bar{2}.260$ and $\bar{2}.272$ differ by about this 3 per cent., and if the first were smaller the percentage difference would be larger.

Chart 4 is calculated from the Harris and Benedict[10] standard multiple prediction tables for normal basal metabolism of adults. It is impossible to put these tables in the form of logarithms. They predict the hourly calories as the sum of two numbers. They are to be used as follows. From the height in inches and the age in years read by interpolation between the family of lines a number corresponding to the lines. From the weight in pounds read on the single line the corresponding abscissa (numbers 20 to 70). The sum of these two numbers is the expected hourly calory production.

Example.—Male, age 35, 62 inches tall, 135 pounds.

(35,62)	23
135	38
	61 predicted hourly calories.

The normal metabolism data of Benedict leaves a gap from the seventeenth to the twenty-first year. It is believed that the data of Benedict more nearly predict the normal than do those of DuBois. The data of DuBois are, however, widely used. They are included here as Chart 5 and Chart 6. Chart 5 plots the logarithms of reciprocal square meters of body surface. It is the same family of curves as that of DuBois.[11] Chart 6, due to the data of Aub and DuBois,[12] gives the logarithm of the reciprocal normal calories per square meter per hour.

Chart 3 is similar to Chart 2. It gives the logarithm of the factor reducing the observed air volume to 0 C., 760 mm. of mercury at latitude 45 degrees and sea level together with a correction to 0 C. of the mercury column and brass scale. It does not correct for aqueous vapor tension as does Chart 2 and is to be used with portable respiration apparatus. The above remarks on corrections for latitude and altitude apply equally to this chart.

Table 3 is a three place logarithm table and Table 4 is a table of antilogarithms. The logarithms of the charts consist of a mantissa, the decimal, which is always positive, and a characteristic, the integer in front of the decimal point which is negative. The signs of the characteristic are to be considered in taking the sum of the various logarithms; the characteristic of the sum is an integer which is the sum of the separate characteristics plus any digit carried to this place in adding the adjoining columns in the mantissae. The mantissa only is used in going to the table of antilogarithms and the characteristic plus one represents the number of integral digits to be pointed off in the number of the table. It fixes the position of the decimal point. In reading from Table 3 the logarithm of a number such as the hourly volume in liters assign to the mantissa of the table a characteristic one less than the integral digits in the number.

Calculation of Calory Production and Basal Metabolic Rate.—The charts are so arranged that the only calculation required is the performance of a sum.

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10. Harris and Benedict: Carnegie Inst. Wash. Pub. No. 279, 1919, p. 253.
11. DuBois, D., and DuBois, E. F.: Arch. Int. Med. **17**:865 (June) 1916.
12. Aub and DuBois: Arch. Int. Med. **19**:831 (June) 1917.

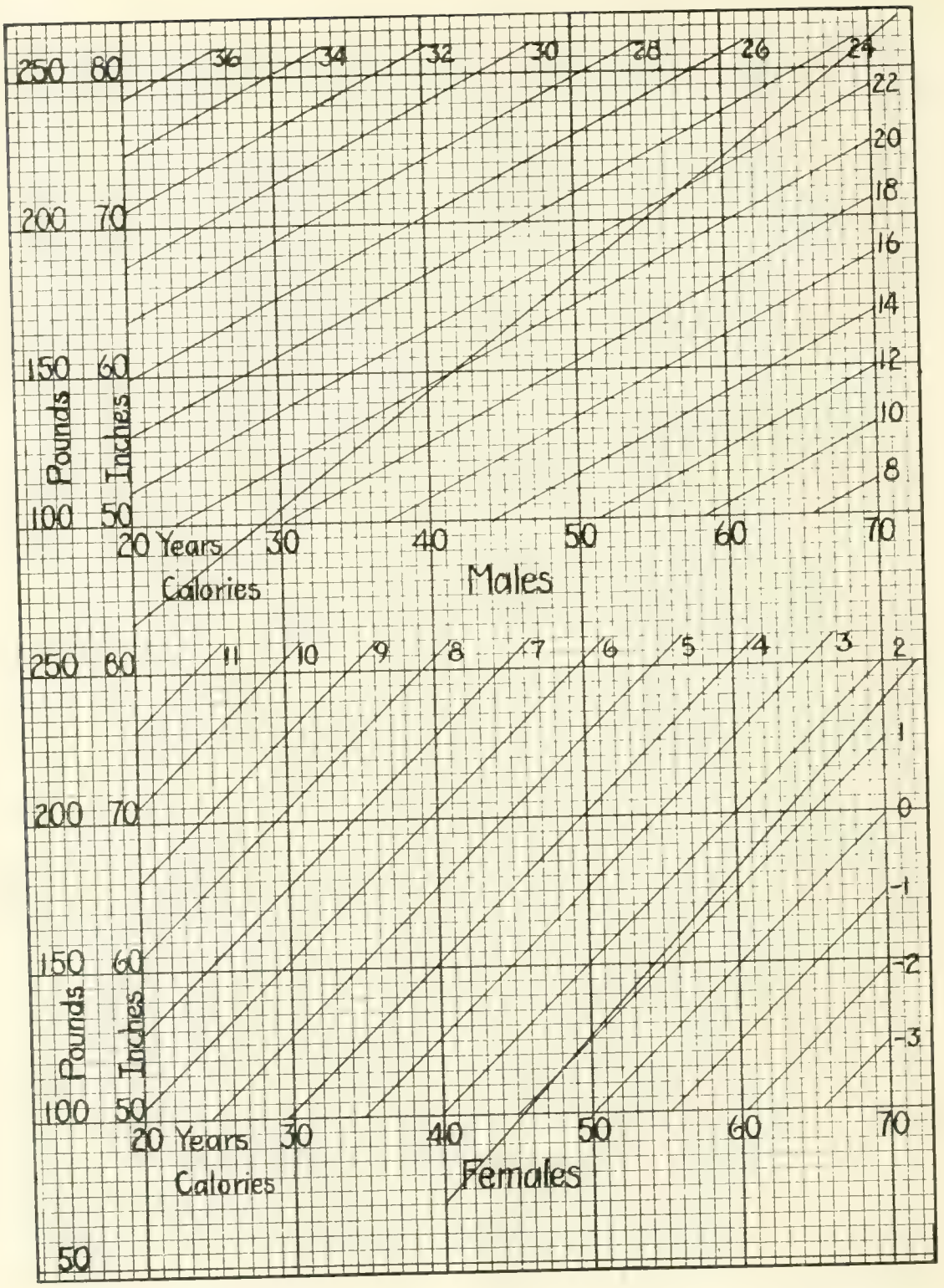

Chart 4.—The chart is based on the standard multiple prediction tables of Harris and Benedict for normal basal metabolism. From the height in inches and the age in years there is read by interpolation between the family of parallel lines a first number. The intersection of the horizontal giving weight in pounds with the single diagonal line gives an abscissa, 20 to 70. The sum of this and the first number is the normal calory production per hour. The tables of Harris and Benedict do not extend to heights below sixty inches.

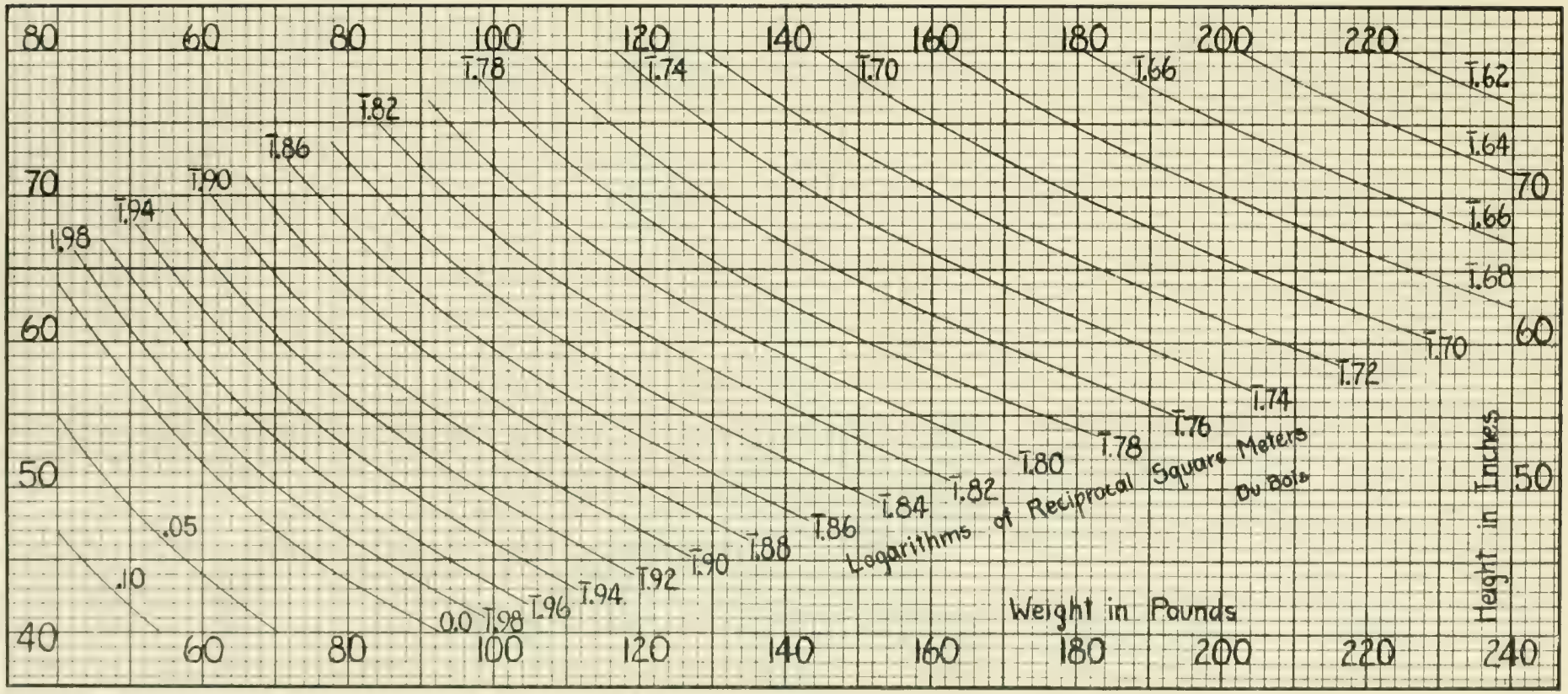

Chart 5.—The ordinates are height in inches and the abscissas weight in pounds. The curves are derived from the DuBois Height Weight formula for square meters body surface. They have been chosen so as to assign as signatures to them logarithms of the reciprocals of square meters of body surface.

To determine hourly calory production:

(a) using the Haldane apparatus.

Add the figures obtained by interpolation from Charts 1 and 2 and the logarithm, from Table 3, of the hourly volume in liters, as read on a meter or spirometer. The antilogarithm, from Table 4, of this sum is the calory production. The respiratory quotient is read directly by interpolation between the lines of Chart 1.

(b) using a direct reading oxygen consumption apparatus (Benedict, etc.).

Add to $\bar{1}.4617$ the logarithm, from Table 3, of the observed oxygen consumption per minute in c.c. and the figure obtained by interpolation from Chart 3. Before going to Chart 3 for the volume correction add to the observed temperature of the bell 1 F. as suggested by Benedict (½ C). The antilogarithm of the sum is the calory production. The respiratory quotient is assumed to be 0.82.

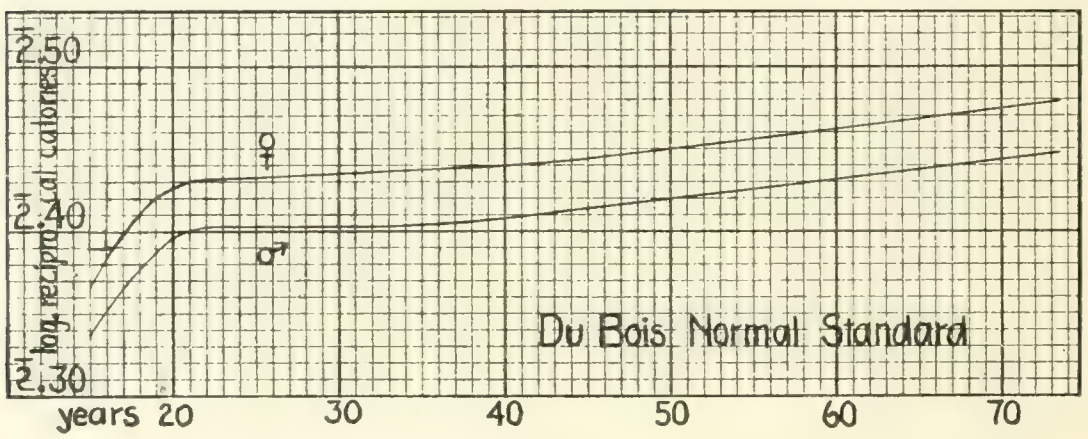

Chart 6.—The curves are the logarithms of the reciprocal of the normal hourly calory production of males and females as given by Aub and DuBois. DuBois data for males under 15 years is omitted, the data of Table 2 being preferred. In the 15 to 20 year interval DuBois data are higher than the data of Benedict. Above 20 years comparison cannot be made simply.

The hourly calory production as determined under (a) or (b) may be compared directly with the normal obtained from Chart 4. The basal metabolic rate is the quotient of the actual by the predicted. In the case of children, the basal metabolic rate determination may be made by simply adding the figure of Table 2 to the sum as obtained above under (a) or (b). The antilogarithm of this sum is then the basal metabolic rate. If it is desired to refer to the DuBois standard, add as a part of the sum the figures from Charts 5 and 6. The antilogarithm of the sum is the basal metabolic rate.

The results are given with no greater error than that inherent in the data. Each chart or table is calculated with a slightly greater degree of accuracy than the data warrant. The charts and tables are such that the basal metabolic rate is given correctly to within one unit in the second decimal place, that is

to within one per cent., and the total calory production correctly to within one-half unit in the second figure. This amount of precision necessitates the reading of Chart 1 to within two units in the third decimal place. This latter may be accomplished by applying a scale between the two CK lines in which interval the point lies and turning the scale diagonally until the ends of a ten unit interval on it fall on the two CK lines. The proportionate distance from the one line to the next of the point to be interpolated is then read off directly from the scale. The error is not over two per cent. when Chart 1 is not so taxed to its capacity. Chart 1 can easily be read more closely than the data can be calculated with a four place logarithm table and more closely than the Haldane gas buret can be read. Chart 4 can be read correctly to one-half calory, Chart 5 can be read to one-half unit in the second decimal place, and the other charts and tables are readily read to three decimals. The logarithm tables are calculated so as to be correct to one unit in the third decimal place.

Example 1.—Haldane readings 97.32 and 79.48. Temperature 20 C.; barometer 751 mm. Hourly volume 452 liters. Male, age 38, height 65½ inches, weight 150 pounds.

Chart 1.	$\bar{1}.19$	R.Q. .83	
Chart 2.	$\bar{1}.9525$		
Log. vol.	2.655		
	1.7975	antilog. 62.7	calories per hour (actual)
		Chart 4. 24	
Chart 5.	$\bar{1}.755$	41.5	
Chart 6.	$\bar{2}.406$		
		65.5	calories per hour (expected)
	$\bar{1}.9585$	antilogarithm 0.909	B. M. R. (Du Bois)

Example 2.—Haldane readings 95.6 and 79.74. Temperature 18 C.; barometer 740 mm. Hourly volume 234 liters. Girl, aged 11, weight 80 pounds.

Chart 1.	$\bar{1}.405$	R.Q. .83	
Chart 2.	$\bar{1}.950$		
Log. vol.	2.369		
Table 2.	$\bar{2}.305$		
	0.029	antilogarithm 1.07	7 per cent. above the normal.

Example 3.—Average reading for contraction of Benedict spirometer bell, per minute 240 c.c. Average temperature of bell plus 0.5 F. (26 C.); barometer 746 mm. Female, aged 32, height 62 inches, weight 125 pounds.

Cal. factor	$\bar{1}.4617$		
Log. 240	2.380		
Chart 3.	$\bar{1}.9505$		
	1.7922	antilog. 62.0	calories per hour (actual)
		Chart 4. 6	
Chart 5.	$\bar{1}.805$	50	
Chart 6.	$\bar{2}.435$		
		56	calories per hour (expected)
	0.0322	antilogarithm 1.08	B.M.R. (DuBois)

SUMMARY

Tables and charts have been prepared by means of which the basal metabolic rate may be calculated by simply adding five numbers.

The charts condense the usual tables into a very small space. They include one reducing saturated gas volumes to 0 C. dry, 760 mm. mercury, sea level, 45 degrees latitude with a temperature pressure correction for the brass or glass scale of the barometer.

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June, 1922, Vol. 29, pp. 748-762

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A NEW OPTICAL INSTRUMENT FOR THE DETERMINATION OF HEMOGLOBIN.

By H. S. NEWCOMER.

(From the Laboratory of the Henry Phipps Institute, University of Pennsylvania, Philadelphia.)

(Received for publication, February 17, 1923.)

In a previous article[1] the author discussed the conditions under which a satisfactory artificial color match might be obtained for hemoglobin or its derivatives. It was shown that there is in fact no satisfactory material matching oxyhemoglobin because of the depth of its absorption bands. These bands are deeper than those of any other known material of similar color. Acid hematin is a substance with a smoother absorption curve. Materials can be found with absorption curves nearly matching the curve of acid hematin and in which the corresponding physiological transmissions are even more nearly equal. Such an equivalent curve was found in one sample of a high transmission yellow signal glass. The matching color so obtained and tested has a greater uniformity in its color value, as judged by different individuals, than has any possible glass selected to match oxyhemoglobin. The hemoglobin value of 1 mm. sections of this yellow glass was carefully determined.

It is the purpose of this article to describe a hemoglobinometer which has been constructed, using this particular yellow glass of known hemoglobin value as a color standard. The principle on which the instrument is constructed is the making of a photometric match between a standard filter of 1 mm. section of this yellow glass on one side, and a sample of blood diluted with 1 per cent hydrochloric acid on the other.

All instruments for the determination of hemoglobin now on the market, with the exception of certain ones using carbon monoxide hemoglobin as a standard, and the Miescher instrument

[1] Newcomer, H. S., *J. Biol. Chem.*, 1919, xxxvii, 465.

which matches oxyhemoglobin, either use materials as standards for which the color value is not determined with any very reassuring accuracy or the materials are not permanent in color. Of the red glass instruments, the Miescher is the only one which seems to be properly standardized. All of the red glass instruments have the inherent spectrometric errors mentioned above.

It has been our aim to produce a precision instrument for the measurement of hemoglobin. We have therefore used acid hematin as the substance to be matched because it is the hemoglobin for which the most exact photometric match can be obtained. The glass used as a standard is permanent in color and the basis on which its hemoglobin figures depend is clearly defined. In conjunction with the Technical Bureau of the Bausch and Lomb Optical Company every effort has been made to perfect the optical qualities of this instrument and, while making a colorimeter of high optical quality and precision, it has been our endeavor to provide a method of reading percentage hemoglobin directly with the least possible manipulation.

The instrument is a modified Duboscq colorimeter of compact design. The body of the instrument (Fig. 1) is of aluminum castings to which are attached the integral parts of the equipment. The rack and pinion actuating the cup table is of the precision microscope type, both cups being operated by the same pinion. To the pinion is attached a drum provided with a spiral groove in which travels a pointer fixed in the table. The calibration is along the margin of the groove on the drum. This arrangement gives a direct reading instrument calibrated in percentage hemoglobin. The individual divisions on the drum are widely spaced and permit easy reading of the result to within 1 per cent. In addition to the feature of accuracy the position of the drum is such as to permit its being easily observed by a slight shift of the eyes from the position at the eyepiece.

The prism system is of double rhomboid type, the inner reflecting surfaces of both rhomboids being silvered. The dividing line of the field is formed by the sharp edge of a silvered reflecting surface. This dividing line becomes practically invisible when the fields become the same color, the fields shade imperceptibly into one another and very delicate and accurate settings are assured.

The standard slip of colored glass is incorporated in the instrument at the top of one of the plungers. By a special process it

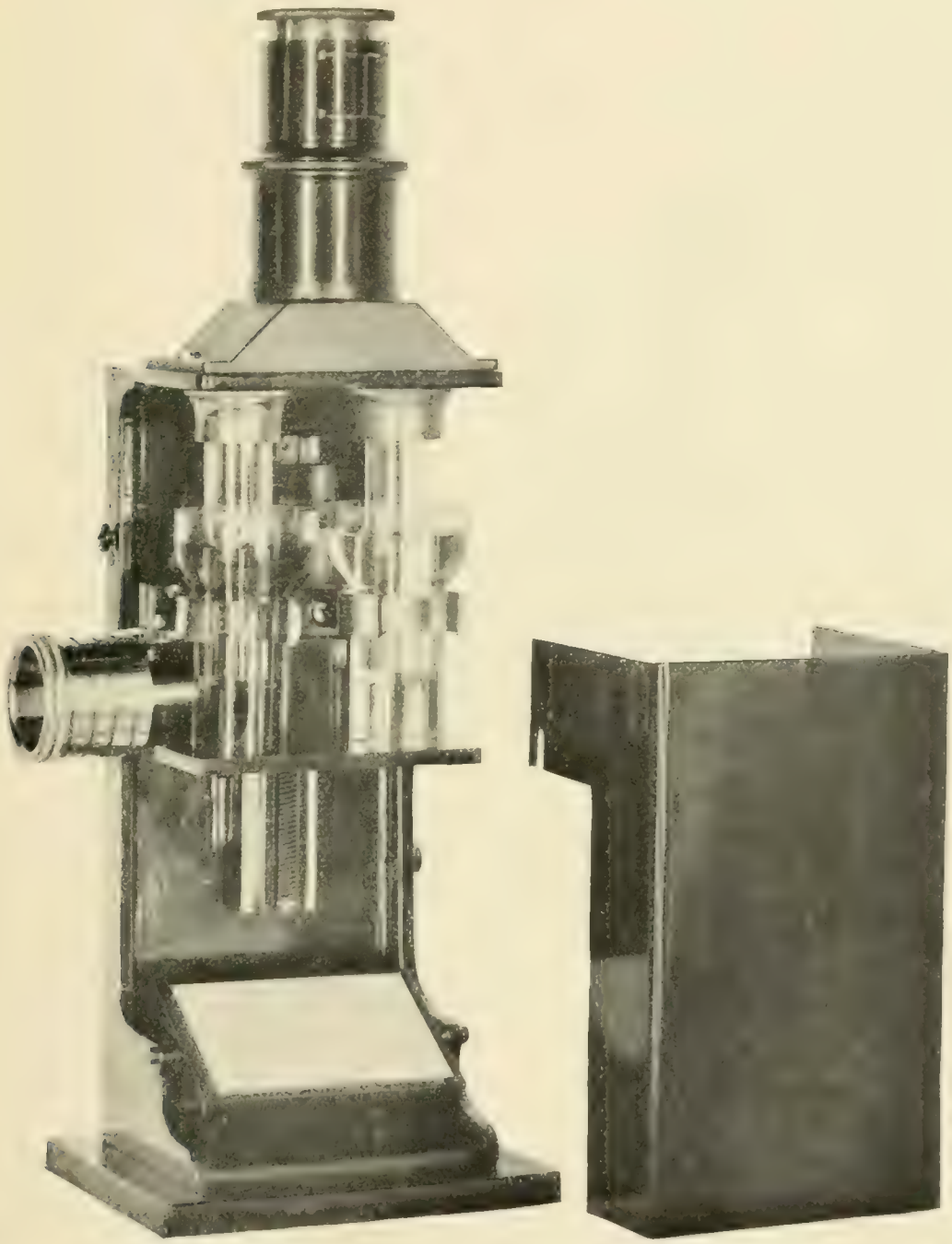

Fig. 1.

is ground and polished accurately to within $\frac{1}{2}$ of 1 per cent of the desired millimeter thickness. The cups are of clear glass

with bases of optical glass fused firmly upon them. Their size is such that they carry the volume contained in the mixing pipette and give with this amount of fluid readings over the entire scale. One of the cups is to be filled with plain water and the other with the blood preparation. The latter is made by diluting 10 c.mm. of blood to 502 volumes with 1 per cent hydrochloric acid. A suitable pipette is supplied with which to make this dilution. At this dilution readings down to 40 per cent hemoglobin may be obtained. For lower values 20 c. mm. of blood in the same pipette are used.

It is possible to adjust the drum to correct position when the plunger is on the bottom of the cup. This adjustment would be necessary if the thickness of the glass bottom of a replacement cup differed from that of the one supplied with the instrument. However, the optical glass used is so uniform that it is unlikely that a new cup will require readjustment of the drum.

The height of the instrument is 8 $\frac{15}{16}$ inches and the weight 2 lbs. 4 oz. and with the case 3 lbs. 7 oz.

The instrument is calibrated to read percentage hemoglobin. The colored glass, as originally calibrated, had a hemoglobin value equivalent to a 1 cm. column of acid hematin solution derived from a 1 in 502 dilution of blood containing 19.08 gm. of hemoglobin in 100 cc.

There were some good reasons for proposing to calibrate this instrument to read hemoglobin in grams, but customary usage determined us to give the figures in percentage and to use as a basis for the standard or normal for 100 per cent the information in the data of Williamson.[2] These data are a collection of very careful determinations of the hemoglobin content of the blood of 919 normal individuals of varying ages living in the city of Chicago. The average figure for the adult males was 16.92 gm. of hemoglobin per 100 cc. of whole blood and this is taken as the 100 per cent of our scale.

Fig. 2 gives these values of hemoglobin for varying age and sex in chart form. Smooth curves have been drawn from the data to which we refer. From the curves one can readily see the range in hemoglobin values with age and sex and the meaning which the percentage figures have.

[2] Williamson, C. S., *Arch. Int. Med.*, 1916, xviii, 505.

When whole blood is mixed with 1 per cent hydrochloric acid a yellow solution of acid hematin results. The color of this

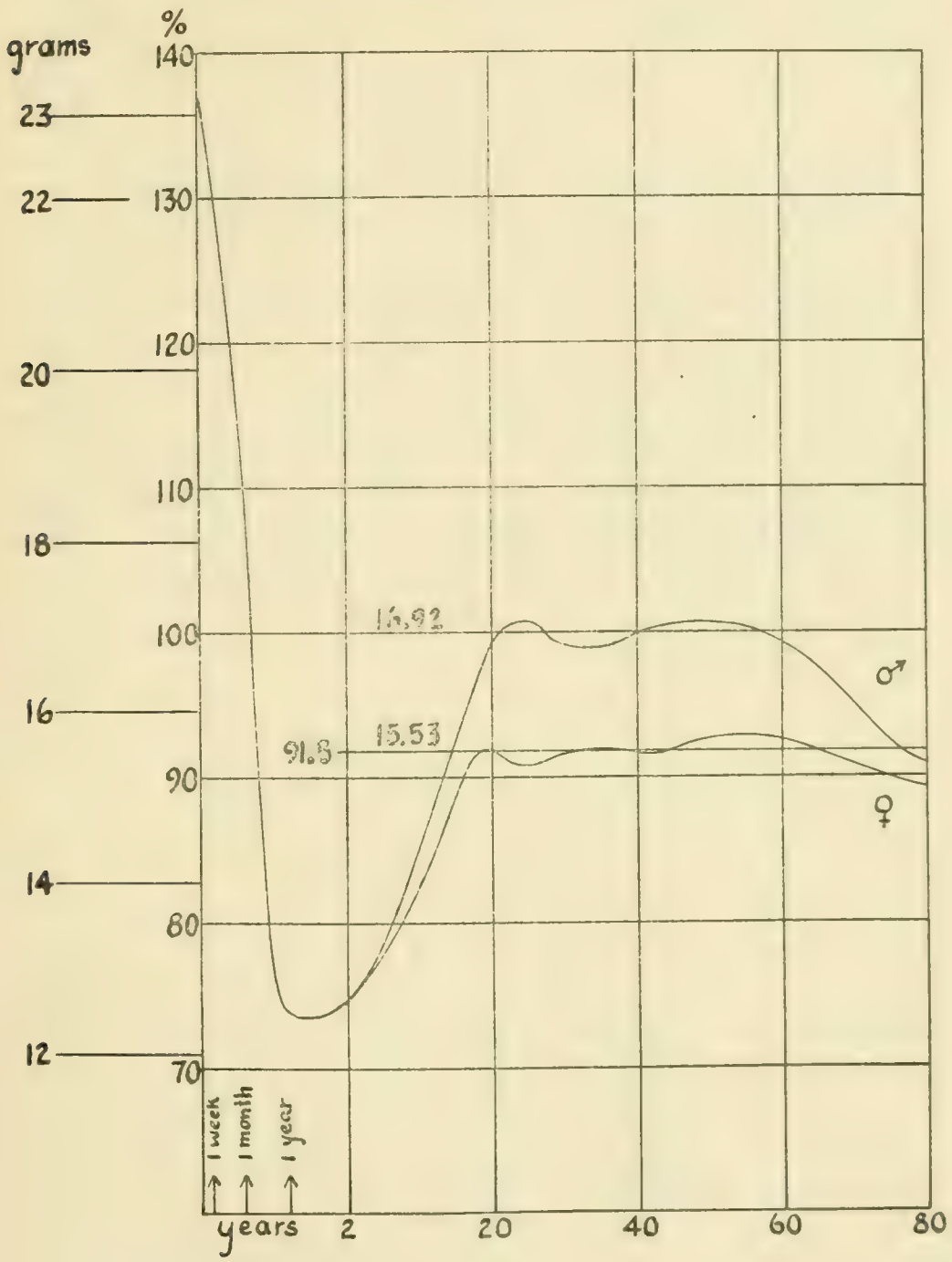

Fig. 2.

solution deepens rapidly at first and continues to deepen with time. It deepens according to a law; namely, the color depth.

at a given time after dilution, falls short of its final value by a percentage equal to $\frac{40}{t}$ where t equals the time since dilution, expressed in minutes. The instrument is calibrated to read to absolute correctness when the color is at its final depth. Theoretically, the color never reaches its final depth and from a theoretical point of view then, the reading is always a little low. However, after the solution has stood for $\frac{1}{2}$ hour the readings are correct to within approximately 1 per cent. If the time elapsing between the making of the solution and the reading is short enough to make this error objectionably large, it can be corrected for by rule or by the use of a table which accompanies the instrument.

The instrument which we have produced and have described is of high optical and mechanical quality. The hemoglobin readings of this instrument are based on well known and reliable data for normals. The result is a precise instrument equipped with a scale of hemoglobin values which are well defined, therefore, permitting accurate readings in figures which in other instruments have been based on uncertain or undefined standards.

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[Contribution from the Laboratory of the Henry Phipps Institute of the University of Pennsylvania]

A SULFONATED NAPHTHYLARSINIC ACID

By A. Elizabeth Hill and A. K. Balls

Received June 12, 1922

In the course of a certain chemotherapeutic research at this laboratory, it seemed advisable to prepare a compound similar in properties to the α-naphthylarsinic acid described by W. Kelbe[1] but more soluble in water. It was reasonable to suppose that this might be obtained by sulfonating the original α-naphthylarsinic acid. A careful review of the literature leads us to believe that only one compound containing both sulfonic and arsenic acid groups on the same nucleus has been prepared. This is the trisulfonic

[1] Kelbe, *Ber.*, **11**, 1503 (1878).

acid of triphenyl-arsenic oxide.[2] Jacobs and Heidelberger[3] have made other arsenic compounds with both an arsenated and a sulfonated nucleus.

For the purpose of obtaining conveniently a quantity of α-naphthylarsinic acid to carry out these experiments, a new method was used which is merely an adaptation of the reaction of Bart,[4] but which, by giving a product of very good quality and by avoiding the preparation, chlorination, and hydrolysis of mercury dinaphthyl, seemed quite suitable to our needs.

Preparation of α-Naphthylarsinic Acid from Napthylamine and Sodium Arsenite. —One mole of α-naphthylamine is dissolved in a mixture of 3000 cc. of hot water and 100 cc. of conc. hydrochloric acid. After cooling to 0°, 200 cc. of hydrochloric acid (sp. gr. 1.18) is added and the α-naphthylamine diazotized in the usual manner with one mole of sodium nitrite. The diazo solution thus obtained is poured into a solution of 600 g. of anhydrous sodium arsenite in 2000 cc. of water.[5]

The best yield was obtained by allowing the diazonium compound to decompose slowly at room temperature. The evolution of nitrogen occupies several days, and when it is complete the liquid is filtered from the brown by-product, and then acidified with hydrochloric acid. The precipitate of crude α-naphthylarsinic acid is filtered off and purified by dissolving in a cold conc. solution of sodium bicarbonate, the insoluble residue filtered out, and naphthylarsinic acid reprecipitated with hydrochloric acid. By recrystallization from water the substance may be purified still further.

On cooling the aqueous solution, the acid crystallizes in a creamy-white mass of needles, melting at 197°. It is soluble in hot water, ethyl and methyl alcohol, and acetone and is insoluble in mineral acids, benzene, carbon disulfide, carbon tetrachloride, chloroform, toluene and xylene. An analysis of material recrystallized from water gave the following results, also showing the material to be free from water of crystallization.

Analyses: Calc. for $C_{10}H_7AsO(OH)_2$: C, 47.62; H, 3.60; As, 29.70. Found: C, 47.45; H, 4.03; As, 29.69.

Preparation of Naphthylarsinic Monosulfonic Acid from Naphthylarsinic Acid

The naphthylarsinic acid prepared as above cannot be sulfonated by employing either diluted or ordinary 98% acid, even though maintained at high temperatures for a long time. The addition of mercury is likewise without effect.

By using fuming (20%) sulfuric acid however, the reaction takes place at once and without the use of external heat or catalyst. A considerable evolution of heat occurs during the reaction which is quite rapid, and accompanied by the immediate separation of the monosulfonic acid in solid form.

[2] Michaelis, *Ann.*, **321**, 186 (1902).

[3] Jacobs and Heidelberger, THIS JOURNAL, **41**, 1610 (1919).

[4] Bart, Ger pat. 250,264, Eng. pat. 568, U. S. pat. 1,061,587.

[5] Using copper powder as a catalyst, the diazo solution is poured into a solution of 192 g. of sodium arsenite in 2000 cc. of water, 200 cc. of 40% sodium hydroxide and 150 g. of copper powder, the subsequent procedure being the same in either case. The yield was 30 g. of α-naphthylarsinic acid, using copper powder, and 50 g. by the method as described above. We see no advantage in the copper powder procedure.

One hundred and fifty cc. of fuming sulfuric acid (sp. gr. 1.9) is poured on 50 g. of naphthylarsinic acid and the mixture stirred; the temperature rises to 80–100°. After stirring has been continued for 5 minutes the temperature falls to about 75° and a gray solid begins to separate. After an hour's time during which the stirring is continued, the mixture (now at room temperature) contains a great amount of solid. It is poured into ice and water (2 liters), also stirred, and after a few minutes the precipitate filtered off. The solid is then best dissolved with sodium hydroxide and, after boiling with charcoal and filtering, the sulfonic acid is precipitated with hydrochloric acid. It can then be recrystallized from boiling water. If the sulfonic acid contains alkaline earths, as is sometimes the case with the use of impure fuming acid, a considerable residue remains insoluble in soda. This generally consists of calcium and magnesium salts of the sulfonic acid and can be conveniently decomposed with hydrochloric acid. The free acid, precipitated on cooling the solution, is filtered off and added to the rest. The yield is about 60% of that theoretically obtainable.

The material has the property, rare among sulfonic acids, of being easily crystallizable, and is capable of being prepared in an almost perfect state of purity. It crystallizes from water in gleaming white plates, is somewhat hygroscopic, and holds its water rather tenaciously. It can be dried in a vacuum or at 100°; no definite amount of water of crystallization was discovered, however. It is easily soluble in hot water, alkalies, acetone, methyl and ethyl alcohol, is difficultly soluble in ether, and is insoluble in mineral acids, benzene, carbon disulfide, carbon tetrachloride, chloroform, toluene, and xylene. It neither melts nor decomposes below 250°.

Calc. for $C_{10}H_7AsO(OH)_2SO_3H$: C, 36.13; H, 2.73; S, 9.66; As, 22.57. Found: C, 35.8; H, 2.54; S, 9.53; As, 22.30.

Alkaline potassium permanganate easily oxidizes the material. After acidifying and removing of the excess of permanganate, a mixture of substances remains easily soluble in both water and alcohol and, therefore, extracted with alcohol from the evaporated residue. The alcohol extracts a thick yellow hygroscopic liquid which contains both arsenic and sulfur, and gives fluorescence tests for the phthalic acid configuration with resorcin and sulfuric acid, showing its derivation from then aphthalene nucleus. Analysis of this liquid showed water, 4.08%; arsenic, 15.90%; and sulfur, 6.75%.

It will be seen that the arsenic and sulfur are in an equimolecular ratio, which again confirms the observation that the original substance is a monosulfonated naphthylarsinic acid.

This behavior on oxidation would no doubt furnish evidence of value in locating the position of the sulfonic acid group on the naphthalene nucleus. It must be remembered, however, that the material obtained from the oxidation is a viscous liquid without a definite melting point, and with no other definite criterion of a pure compound. It may, therefore, well be a mixture of several substances resulting from the oxidation. On mixing the oily liquid with water, an acid solution results. A few attempts to prepare crystalline salts from the substance were made unsuccessfully, and of course

until this is done, nothing can be said in this connection concerning the location of the sulfonic group acid.

Three potassium salts have been prepared from the sulfonic acid by adding the calculated quantities of potassium carbonate. The monopotassium salt, the only one recrystallized for analytical purposes, showed arsenic, 20.19%, and potassium, 10.86%, which compare quite closely with values calculated for a monopotassium salt of naphthylarsinic monosulfonic acid, namely, arsenic, 20.25%, and potassium, 10.53%.

Potassium was determined by dissolving the potassium salt in water, precipitating the greater part of the sulfonic acid with strong hydrochloric acid. After filtering this off and washing with dil. hydrochloric acid the potassium was easily determined in the filtrate by the perchlorate method,[6] finally washing the potassium perchlorate with 98% alcohol containing a little perchloric acid.

The small amounts of sulfonic acid not precipitated by the hydrochloric acid are oxidized by perchloric acid to alcohol-soluble substances. Control mixtures of 0.4660 and 0.4712 g. of pure potassium carbonate with 0.5 g. free sulfonic acid, respectively, were run to test the applicability of the method; weights of potassium added as carbonate were 0.4660 and 0.4712 g., the weights recovered as perchlorate 0.4652 and 0.4710 g., respectively.

The method is interesting as affording a very easy method for the determination of potassium in a few classes of organic compounds where the oxidation products formed by perchloric acid are soluble in alcohol.

All the potassium salts are white crystalline solids easily soluble in water.

Summary

1. α-Naphthylarsinic acid has been prepared by diazotizing α-naphthylamine and then treating with sodium arsenite.

2. Upon treatment of α-naphthylarsinic acid with fuming sulfuric acid a monosulfonic acid of α-naphthylarsinic acid is produced.

PHILADELPHIA, PENNSYLVANIA

[6] Morgan, *J. Ind. Eng. Chem.*, **13**, 225 (1921).

THE EARLY DEVELOPMENT OF THE CORNEAL TUBERCLE. (A STUDY IN SLIT LAMP MICROSCOPY.)

By Drs. BERTHA T. HAESSLER and F. HERBERT HAESSLER.

(From the Henry Phipps Institute of the University of Pennsylvania, Philadelphia.)

EXPERIMENTAL tuberculosis of the cornea has been studied repeatedly and both the gross and microscopical appearances of the lesions have been accurately described. In 1877 Cohnheim and Salomonson (1) inoculated tuberculous matter into the anterior chamber and called attention to tuberculosis of the iris and cornea. Haensell (2) in 1879 inoculated the pus from tuberculous joints into the cornea of rabbits and guinea pigs, and describes the gross and microscopic appearance of the lesions which, in his cases, all went on to complete healing. Panas and Vassaux (3), in 1885, likewise gave an accurate picture of tuberculosis of the cornea with healing, gross and microscopic. They passed tuberculous sputum through guinea pigs and used the ground-up tubercle, which was introduced into the cornea with a vaccine stylet. Kostenitsch and Wolkow (4), in 1892, used pure cultures of the tubercle bacillus for the study of experimental tuberculosis of the cornea, anterior chamber, and vitreous. Their work is almost entirely a histological study of the cellular reactions to the tubercle bacillus. In 1896, Heydemann (5) published an

extensive dissertation on tuberculosis of the cornea with a thorough review of the literature on the development of the tubercle. He described both gross and microscopic changes. The first reaction was observed to occur at the end of ten to fourteen days, and healing eventually took place in all cases. Schieck (6), in 1896, gave a detailed and interesting account of the first stages of experimental tuberculosis of the cornea of the rabbit, as observed in microscopic sections, with an introductory discussion of the literature. Bach (7) likewise described tuberculosis of the cornea both clinically and experimentally, and found that if a deep corneal inoculation was made, tubercles developed more slowly than after superficial inoculation. He saw a secondary involvement of the iris in only one instance. Krusius (8), in 1911, did considerable work on experimental tuberculosis of the eye. He attempted to obtain quantitatively comparable results by using large series of similar animals, with one culture of constant virulence. The quantity of organisms was standardized by emulsifying dry bacilli in salt solution and making dilutions with large differences made of the same emulsion. He inoculated his emulsions into the corneal substance, and used a corneal microscope as an aid to his observations. He concluded that the incubation period in a given case is inversely proportional to the quantity of the infection, with an upper limit at which the incubation period equals zero and a lower limit where it equals infinity. He states that only in the rarest cases do the bacilli enter the general circulation. He found, by using quantitative inoculations, that the susceptibility of the eye to tuberculosis was, decreasingly as follows: vitreous (most susceptible), aqueous, cornea, conjunctiva, and lens. Krusius, as well as all the other workers here quoted, obtained healing in practically all the cases studied.

Lewis and Montgomery (9), 1914, published a paper entitled "Experimental Tuberculosis of the Cornea," and it is on this work that the present study is based. Our study was undertaken at the suggestion of Dr. Lewis with the idea that something might be added to the observations of the gross development of the tubercle by the aid of the corneal microscope with slit lamp illumination. The technique of inoculation is that described by Lewis and Montgomery, namely, injection into

the corneal stroma of an emulsion of tubercle bacilli by means of a small record syringe and a number 26 platinum needle with a very short bevel and a sharp point. Rabbits were used exclusively and the eyes were well cocainized before inoculation. Grossly the lesions developed as described by Lewis and except where a known avirulent organism was used, healing at no time occurred. The animal eventually succumbed to a generalized tuberculosis. Emulsions made of pure cultures of bovine strains of known virulence were used in all cases.

In the majority of the animals our studies were limited to the early changes—those occurring during the first, second, or third weeks after inoculation—as we found that it was here that the slit lamp and corneal microscope were of the greatest help.

The Gullstrand slit lamp is an instrument that has increased the field of usefulness of the microscope for observing the living eye, not because its light is more intense but because it is corrected so that only a narrow accurately delimited beam of light is focussed onto any structure of the eye, while other parts remain in relative darkness. The contrast between the illuminated and contiguous unilluminated areas then permits microscopic study of fine details which had previously escaped observation.

The source of light is a small, closely wound Tungsten spiral enclosed in a nitrogen-filled bulb. A condenser consisting of two plano-convex lenses, placed with the convex surfaces toward one another, projects an image of the spiral into the diaphragm of the objective lens—plano-convex with the convex surface toward the light—of 7*cm* focal length, which condenses the light to form an evenly illuminated surface less than 1*mm* wide.

In the model of the Gullstrand slit lamp manufactured by Zeiss, the lamp is mounted independently on an extensible stand. The eye can be observed with the Czapski corneal microscope similarly mounted, and magnification varying between eight and one hundred and eight diameters may be used. The oscillation of the living eye precludes the use of higher magnification than this.

This armamentarium makes it possible to scrutinize the individual cells of the endothelial layer of the cornea, to see

single cells and agglutinated masses of cells in the aqueous humor, to see circulation of blood corpuscles in the finest capillaries, to see nerves in the cornea, to see structures in the vitreous, and to localize precisely the position of structures observed in the clear media of the eye.

Our studies may be roughly divided into two groups; one, the early development of the corneal lesion in healthy rabbits, which constitutes the major portion of the work, and second, the early changes observed in the eyes of animals previously inoculated with small doses of tubercle bacilli and, therefore, suffering from tuberculosis. These we hope to discuss in a second paper.

After the work was well in progress, white rabbits only were used. Slight vascular changes were found to be easier of detection in albinos and changes occurring at the limbus as well as in the iris were better seen. The rabbits weighed from 1500 to 2500*gms* and in each case the eyes were carefully examined with the slit lamp and microscope before inoculations were begun. Aside from tubercle bacilli, of which two virulent and one avirulent strains were used, comparative studies were likewise carried out on a small number of rabbits with, first a virulent twenty-four-hour culture of staphylococcus aureus and, second, an emulsion of mercury sulphide in water. In so far as possible, these have been correlated with the main problem.

First Changes Observed.—Of the twenty-six rabbits studied, the first pathological change was observed four days after inoculation in twelve rabbits, three days after inoculation in seven rabbits, two days in three, and in one case each, five, eight, nine, and eleven days after injection. The time depends not so much on the virulence of the culture used as the method of inoculation and the number of bacteria introduced. In all cases where reaction occurred after the fourth day, the culture used was a virulent bovine strain. A superficial scratch and a weak suspension were used in the rabbits that showed the first change on the fifth, eighth, and ninth day respectively. In the case where the reaction occurred on the eleventh day, a deep inoculation of a virulent culture was made. No explanation for the delay can be offered except that of the varying susceptibility of different animals.

In the great majority of rabbits, the first change observed was a very faint injection of a leash of conjunctival vessels at the limbus. In the white rabbits, there could always be seen at the same time a pronounced accelleration of the circulation at the limbus. Not only were the vessels dilated but the blood flowed through them with much greater rapidity. In all the white rabbits where a virulent strain of bacilli was used, an injection of the small vessels of the iris preceded or accompanied the limbus hyperæmia. This early injection of the iris vessels was noted by Schieck in his studies in 1896 (Schieck—*Ziegler's Beitrage*, xx., p. 275). In the brown-eyed rabbits this change was overlooked, or possibly impossible of detection on account of the pigment of the iris. In no case of tuberculosis were cells seen in the aqueous preceding the vascular dilatation, though they were often seen simultaneously. When staphylococcus aureus was used, on the other hand, the cellular exudation was much more pronounced than the vascular reaction. In these cases, circulation could not be studied due to the intense œdema and clouding at the limbus. In the rabbits injected with staphylococcus aureus the first change was noticed in twenty hours, and probably was present even earlier. It consisted of an intense vascular injection together with œdema and severe purulent exudation.

Four eyes were injected with mercury sulphide, two of them, where larger amounts were used, showed injection of the vessels of the bulbar conjunctiva within twenty-four hours. In the other two, where smaller amounts of mercury sulphide had been used, the first change was noted on the fifth and sixth day respectively, and consisted of a very slight bulbar injection accompanied by cellular exudation. In none of the eyes where mercury sulphide had been injected was there a pronounced accelleration of the circulation at the limbus.

Cellular Exudation.—The study of cellular exudation proved to be of special interest. Cells are seen in the aqueous in the dark area between the two beams of light reflected by the cornea and iris respectively, and appear as bright glistening bodies (Tyndall effect). When the anterior chamber is very full of cells, the impression is that of a snow fall in a heavy wind. Cells on the lens surface appear as small whitish dots under the lower power, somewhat as white blood cells in the

counting chamber. Under the high power, the cells look white and perfectly round, with a homogeneous protoplasm. It is generally impossible to distinguish a nucleus. It is always easy to tell whether a deposit consists of one single cell or of an aggregation of cells stuck together. Pigmented cells are about two to three times as large as white cells.

On the iris, cells are seen with difficulty and only when they are very abundant can they be made out as small grayish-white bodies. Cellular deposits are readily seen on Descemet's membrane by focusing the microscope through the dark side of the prism which the slit lamp cuts out of the cornea. They appear as single or multiple white dots.

An exudation of small white cells, with a small admixture of larger pigmented cells in the brown-eyed rabbits, occurred anywhere from the third to the eighth day after inoculation. At times a few cells—not more than six—were seen on the lens as early as forty-eight hours after the injection. In 50% of the cases, cellular exudation was first seen on the fourth day. The cellular reaction was in all cases accompanied by hyperæmia of the bulbar conjunctiva. In some cases this hyperæmia preceded the exudation of the cells by twenty-four hours.

The extent, duration, and character of the cellular exudation differs depending on whether a virulent or relatively avirulent strain of tubercle bacilli is used. In the case of a virulent culture, the eye which has been entirely normal at the preceding examination, grossly shows a slight bulbar injection, accompanied or preceded by an intense injection of the small vessels of the iris. Microscopic examination shows the aqueous densely filled with small white cells. These cells are all single and float through the aqueous irregularly; in some cases there is a tendency to drop down into the chamber angle. A large number of cells settle out on the anterior surface of the lens. On the first day the lens is simply peppered with cells without any definite arrangement. On the following day or days there is often seen a distinct tendency to group formation, the denser grouping usually taking place toward the periphery of the lens. Later there is an agglutination of a number of cells which float free in the aqueous or adhere to the lens surface. The clumps may consist of only three to four cells, loosely adherent, or of ten to twelve, or more. In five cases a few clumps were

observed on the first day that cells were seen; in four cases, twenty-four hours later; in two cases forty-eight hours later; in two cases four days; and in one case six days after cells had first appeared. In all the cases that progressed to destruction of the eye, a grossly visible hypopion was eventually formed which consisted of piled up cells in the lower angle of the chamber. Whenever hypopion was seen it was associated with an aqueous full of cells.

Cellular deposits on Descemet's membrane were seen easily when a virulent culture was used. In five cases these deposits occurred on the same day that cells were first observed, in the other cases they were seen two to eight days later. In most cases these deposits were first noticed in the most dependent part of the cornea as distinguished from the deposits on the lens, whose distribution was entirely irregular. Special note should be made of one case where the deposits on Descemet's membrane were definitely grouped about the lesion at the site of inoculation. The opacity roughly vertically bisected the pupil. The lowest part of this opaque area was heavier than elsewhere and it was in opposition to this portion that the cellular deposits were grouped. The deposits were largest and most numerous just beneath the opacity and became progressively smaller and less numerous in the surrounding zone. They could not be seen with the microscope by illumination other than that of the slit lamp, nor were they visible with a + 16 or a + 7 lens of the ophthalmoscope.

When a relatively avirulent strain of bacilli is used, the primary result is practically the same, provided the emulsion of organisms is a sufficiently heavy one. A thin emulsion produces either no reaction whatsoever, or at most calls forth a very small number of cells. When a heavy emulsion is used, the aqueous and anterior surface of the lens are peppered with cells three or four days after inoculation. Within twenty-four to forty-eight hours all cells have disappeared from the aqueous and only a few are left on the lens surface. None are at any time found on Descemet's membrane. Cellular studies with an avirulent culture were carried out on six rabbits. In three of them the disappearance of the cells from the aqueous closed the pathological picture and the eye returned to normal. In three other rabbits short strands of new-formed vessels de-

veloped on the cornea. In two of these cases the vessels appeared twenty-four hours after the cells were last seen in the aqueous; in the other case the corneal vessels were first seen on the last day that the cells in the aqueous persisted. Clumping together of the cells was observed in all these cases on either the first or the second day after the cellular reaction began.

Cellular Reaction with Staphylococcus Aureus.—For the sake of comparison, two rabbits were inoculated intracorneally with an opaque emulsion of a twenty-four-hour culture of staphylococcus aureus. Within less than twenty-four hours there was a thick purulent exudation from the eyelids and the entire cornea was grossly dull. The aqueous was packed with white cells, as was also the lens surface. Many of the cells formed loose clumps. Some of them were adherent to Descemet's membrane. The following day the eye grossly looked much less angry. In one of the rabbits the cells had, to a large extent, disappeared, a moderate number of single cells remaining in the aqueous and on the lens surface. In the other rabbit the cells disappeared less rapidly. For two days the aqueous was packed with cells which settled out to form a hypopion. Three days later, however, this could no longer be seen, nor did any cells remain in the aqueous or on Descemet's membrane. Both rabbits showed a sprinkling of white cells on the lens surface which persisted until three weeks after inoculation.

To determine the part played by mechanical irritation only, four eyes of normal white rabbits were injected with mercury sulphide—a finely granular red powder. It is impossible to control the exact amount of material injected and it so happened that two of the eyes received a large injection, while in the other two a moderate amount only was introduced. In both eyes where the mercury sulphide was in heavy suspension, there was a bulbar injection within twenty-four hours and an occasional cell was seen on the lens. On the second day in one eye, on the third in the other, the anterior chamber was densely filled with cells and cells were seen on the lens, at first single, one to two days later in clumps, then single again just before their disappearance, one week after inoculation.

In the two rabbits where smaller amounts of mercury sul-

phide were introduced, the first reaction occurred on the fifth day in the one, and on the sixth day in the other. In both these cases the cellular exudation, together with a very faint bulbar injection, was the first sign of pathological change. The first rabbit at no time showed any injection of the conjunctiva or iris vessels, dulling of the cornea or other changes. Had the cells not been seen with the microscope, the eye would have passed as normal. Forty-eight hours after the primary exudation, clumped cells were seen in both rabbits, chiefly on the lens surface. Three days later all cells had disappeared from the lens and aqueous in the one rabbit, and only a faint sprinkling on the lens was seen in the other.

New Formed Vessels.—The formation of vessels is perhaps the most characteristic of the lesions seen in tuberculosis of the cornea. Its gross features have been accurately described by various investigators (2, 3, 5, 8). The earliest vessels are always observed at the limbus above, no matter where the corneal injection is made. These vessels usually attain a greater length than those coming in from below or from the sides, and eventually extend into the opacity at the site of injection. In the most advanced stages the entire cornea may be vascularized.

The new-formed vessels are generally first seen on the fifth to the seventh day. Occasionally the earliest strands can be detected on the fourth day, in one case they did not appear until the ninth day and in two until the eleventh day after the inoculation was made. In these latter cases, however, the incubation period has been unusually long. As a general thing it may be said that the earliest vascular shoots on the cornea are seen two to three days after the first signs of reaction have occurred. These shoots develop as short strands coming off from the superficial conjunctival vessels at the limbus and lie superficially on the cornea throughout their course, forming a sort of fringe at the limbus. At the time of their origin the cornea underlying them is clear. After 2–3 days of an irregular central-ward growth, strands of these vessels meet to form capillary loops, through which an exceedingly active circulation is maintained. As the vessels became larger they assumed a broom-like growth and increase in width as well as in length. The vessels just above the site of inoculation are of the greatest

length and eventually extend into the opacity, while the other vessels have formed short loops only.

When a virulent culture of tubercle bacilli is used the vessels develop more rapidly than when an avirulent strain has been injected. In the former case the vessels within three or four days become so large and the cornea becomes so dull that further slit lamp study is impracticable. Blood vessel formation is best studied when an avirulent culture is used and very short strands develop on a clear cornea. When the straight shoots first form, no circulation can be seen in them, but as soon as the strands are joined into loops, active circulation begins. From other loops further strands develop while the primary trunks increase in size. At most a small fringe of capillaries is visible to the naked eye and the vessels never reach into the inoculation site. When the avirulent strain is used, when healing begins, the circulation through the capillaries gradually becomes much slower and soon the vessels are grossly invisible, though microscopically they are still seen to carry a fine current of blood. The smallest capillaries permit the cells to pass by in single file only. In the most distal portions some of the loops become constricted off, at first show stagnant blood and later are obliterated entirely. In our experience the proximal loops have never completely disappeared, though they have been grossly invisible. When such an eye is re-injected, or otherwise irritated—by the introduction of O. T. into the sac, for example—the blood flow through these capillaries is increased and they can again be seen with the unaided eye as a fringe of newly formed vessels.

Although vessel formation is particularly striking in response to the tubercle bacillus, it can also occur after mechanical injury or injection with other organisms. Börri (10) in 1895, showed that after mechanical erosion of the cornea, or injection of mercury bichloride or hydrochloric acid, newly formed vessels developed from the limbus and extended into the dulled area. In our series where mercury sulphide had been injected, very short loops of newly formed vessels developed in the two cases where a heavy emulsion was used and failed to develop in the two where smaller amounts of the mercury had entered the cornea. With the staphylococcus aureus active vascularization took place in all cases, extending from above well into

the area of inoculation. A fairly active circulation was maintained and persisted throughout the period of observation (10 weeks). Here it was interesting to observe that the veins were much more numerous than the arteries and at least three times as wide in diameter.

Changes in the Cornea.—The structure of the normal cornea as seen with the slit lamp and corneal microscope has been described by Koeppe (11) in his book entitled *Die Mikroskopie des Lebenden Auges*, and is pictured by Vogt (12) in his book, *Atlas of Slit-Lamp Microscopy*. When an emulsion of tubercle bacilli—or other foreign matter—is injected into the corneal stroma, a diffuse grayish-white opacity is formed, which fades within five minutes so as to be almost imperceptible. Microscopically it consists of an irregular gray granular area, lying at varying levels of the cornea and showing an epithelial defect at the point where the needle entered. At times instead of the grayish-white opacity described above, a heavy white lesion composed of short parallel lines results. Such an opacity consists of roughly square areas, each made up of 4–6 parallel lines. On a level just above or below such a square is another whose lines run at another angle which may be a right angle or as small as 15°. By superimposing these squares at different levels, the opacity is produced. This opacity does not fade within five minutes but appears practically unchanged in fifteen minutes. Within 18 hours it differs from the usual lesion only in its tendency to long finger-like projections extending from the main opacity into the surrounding tissue. The further course of the two lesions is otherwise identical. The large white opacity cannot be produced at will, but occurs only as a rare accident, in our series twice in 40 cases.

For the first 3 to 6 days the opacity at the site of inoculation remains unchanged. It has an irregular but well-defined outline and a distinctly granular appearance, dependent on the accidental grouping of the masses of organisms injected. The epithelial defect due to the needle puncture gradually disappears within twenty-four to forty-eight hours. On anywhere from the 4th to the 7th day (with occasional cases as early as the 3d, and one as late as the 12th day) the opacity begins to lose its definite edges and its granular appearance. The cornea immediately beneath and surrounding it becomes white and

opaque and the edges of the lesion blend with the surrounding tissue, while the opacity itself changes from a grayish granular to a fluffy yellowish white homogeneous mass of cotton-like appearance in which, within 2 to 3 days, a granular structure can no longer be made out. At this time there is usually a halo of less dense opacity about the central heavy yellowish-white area. Still later this mass breaks up into numerous small white lesions, lying peripherally and grouped as satellites about a larger central yellowish-white area. These are the miliary tubercles so characteristic of the advanced stages of corneal tuberculosis. At the time that the breaking up into small masses occurs, the vessels extend well into the opaque area and ulceration usually begins.

The course of events above described is that which takes place when the lesion goes on to ultimate destruction. In case healing occurs, the fluffy white mass soon regains its granular look and is definitely walled off from the cornea surrounding it. These changes were best studied in the rabbits injected with mercury sulphide, as the breaking up of the red masses can be more easily followed than that of the pale bacillary emulsions. In these rabbits no changes occurred in the dense red masses infiltrating the cornea until after the acute exudation of eucocytes had ceased and the surrounding cornea had been heavily infiltrated with cells. There then occurred a gradual breaking up of the dense red areas into smaller, more granular masses, especially at the periphery. For some distance about the injection site the cornea showed small foci of red granules. Where the mercury sulphide had extended along dense lines, these lines became broken and eventually assumed a dotted appearance. The dense central masses were, however, largely unaffected. Apparently none, or at best very little, of the mercury sulphide was removed, for the red areas appeared to be quantitatively the same when healing was complete as when first injected. The arrangement, however, was of a more broken and granular kind. Ten weeks after inoculation they persisted unchanged, though for the past 8 weeks the eye had otherwise been entirely normal.

A healed tuberculous or staphylococcus infection leaves a grayish granular opacity with well-defined boundaries, in a normal cornea, which persists indefinitely.

Occurring simultaneously with the changes in the opacity at the inoculation site, or perhaps shortly thereafter, the cornea loses its normal glistening appearance and becomes infiltrated with white cells. The part of the cornea first involved is that immediately surrounding the point of inoculation. Soon afterwards, or occasionally at the same time, the cornea becomes cloudy at the limbus above and shows a great increase in white dots—probably an infiltration with wandering cells. This dullness rapidly spreads so that within a few days the entire cornea is opaque.

DISCUSSION.

In a general way our results may be said to agree with those of other investigators, with the exception, however, that in every case we have been able to observe changes earlier than any hitherto reported. This is due partly to the slit lamp method of examination by means of which slight changes can early be seen, and partly to the fact that we used cultures of great virulence for rabbits. Nevertheless, we cannot get away from the fact that after the introduction of tubercle bacilli there is a latent period during which no reaction occurs, which is more definite and prolonged than when a simple foreign body or a pyogenic organism is used.

The stages during which we followed the tuberculous lesion were largely exudative. The question of the origin of cells into the aqueous has always been a matter of speculation. It is our belief that the extreme dilatation of the small iris vessels, observed prior to the cellular exudation, might permit the passage of wandering cells from these vessels into the anterior chamber. We have at several times seen a severely congested iris on the evening of one day, and the following morning have found the aqueous full of cells. We do not wish to infer, however, that the iris is the only possible source of cells in the anterior chamber. The cells in the primary exudation are probably largely leucocytes; in appearance they resemble the cells found after foreign body injection. Puncture of the aqueous, carried out in one case, showed the presence of polymorphonuclear leucocytes only. This cellular reaction, there-

fore, is not specific, but is simply due to foreign body stimulation.

After a time, however, this first active exudation of cells into the aqueous subsides and there are seen smaller numbers of cells chiefly on the lens surface and on Descemet's membrane which we believe to be lymphocytes.

The settling out of these precipitates on the lens has been often observed by ophthalmologists and has been attributed by them to the mechanical factor that man sleeps on his back. It was, likewise held, especially by Straub (13), that the clumps of cells on the lens and on Descemet's membrane were the result of a chance piling up of single cells. We have been able to show that the cells form loose clumps in the aqueous and float on to the lens or Descemet's membrane as a raft, as has been Fuchs' (14) assertion. That there is some specific substance in the lens which attracts cells toward it seems probable. Cells are never found on the iris when the aqueous is clear, but are often seen on the lens. In the rabbit, of course, there could be no purely mechanical sedimentation on to the lens, though sedimentation does undoubtedly occur on Descemet's membrane in the chamber angle. At times, however, precipitates are seen on Descemet's membrane in the small area about the primary lesion, and here too there may be some unknown substance which causes a migration to this area.

Lewis and Montgomery called attention to the significance of the exudation in tuberculosis and have remarked that if it were possible to prevent the exudation entirely, blood vessels would presumably never develop. We can confirm this in another way. The disappearance of the cellular exudation was in every instance the precursor of healing. On the other hand, while the exudate persists there is progressive destruction of the eye.

In connection with the new formation of blood vessels, it should be noted that increased circulation through existing vessels antedated the development of new capillaries and that a slowing of the blood stream was a sign that healing had begun. These phenomena must occur in response to some definite stimulus given out by the infecting organism or its product.

The fluffy white masses which we have observed in the cornea about the injected area resemble precisely the appear-

ance of the fibrinous exudate which is often seen in an otherwise transparent retina. We may, therefore, assume that the cotton-like appearance of the corneal lesion is likewise due to exudation about the point of injection. The clouding of the cornea itself takes place first about the site of inoculation and at the limbus above. The time of its appearance and the fact that it occurs primarily and most markedly in the areas where there was the most abundant blood supply, seem to indicate that the first corneal clouding results from infiltration of the stroma by wandering cells and that proliferation of the fixed tissue cells occurs only at a later date.

Our observations thus lead us to the conclusion that exudative inflammation is the first and most important tissue reaction in response to tuberculous infection.

SUMMARY.

1. The slit lamp and corneal microscope offer a valuable method for the experimental study of fundamental pathological processes as they take place in the living tissue of the eye.

2. In the study of experimental corneal tuberculosis produced by inoculation of emulsions of virulent bovine strains, the first change is seen most commonly three to four days after injection, and consists of congestion of the vessels of the iris and of the bulb, with an increase in the volume and speed of the blood flow.

3. After one injection of virulent tubercle bacilli, cellular exudations of white and pigmented cells occur within 3 to 8, usually 4, days. The cells are seen in the aqueous, on the lens surface, and on Descemet's membrane, at first single, later grouped, then clumped. Eventually the cells drop into the chamber angle and form grossly visible hypopion. When an avirulent culture has been used, cells are seen in the aqueous and on the lens three to four days after inoculation. They occur singly or in small clumps, disappear entirely within 24 to 48 hours, and are never found on Descemet's membrane.

Twenty-four hours after inoculation with staphylococcus aureus, the anterior chamber is densely packed with white cells, single and clumped, which settle out on the lens in the chamber angle, and on Descemet's membrane. Within one to

three days all cells disappear except for a small sprinkling on the lens which persists for 3 weeks.

After injection of large amounts of mercury sulphide, the anterior chamber and lens are packed with cells 2 to 3 days after inoculation. These persist for one week and occur at first singly, then in clumps, and finally singly again. When smaller amounts are used, the first cellular reaction takes place on the 5th to 6th day, and all cells disappear in 3 days.

4. Corneal vascularization occurs after any sufficiently severe irritation of the cornea. It is most characteristic in tuberculosis. New formed vessels arise on the 5th to the 7th day after inoculation. They begin as straight shoots which later form loops through which a very active circulation is maintained. Vessels are best studied after the introduction of avirulent tubercle bacilli. When healing occurs the new formed vessels become grossly invisible but persist as very fine capillaries microscopically. After irritation they become filled with blood and can again be seen grossly.

5. Inoculation of an emulsion of tubercle bacilli into the cornea causes the formation of a gray, granular opacity which fades within five minutes, or of a dense streaked white opacity which persists unchanged after 15 minutes. After 4 to 7 days this opacity becomes yellowish-white and fluffy, and eventually is broken up into miliary tubercles with ulceration. If healing occurs the gray granular appearance again replaces the white fluffy opacity, the surrounding cornea and the cornea at the limbus above is infiltrated with white cells and becomes dull and opaque.

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DORSET'S EGG MEDIUM FOR THE CULTIVATION OF TUBERCLE BACILLI, AND ITS MODIFICATIONS

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The experience of years has shown that the only culture medium with which it is possible to obtain primary cultures of the tubercle bacillus consistently is the egg medium as proposed by Dorset or some one of its modifications. This method was to mix thoroughly the whites and yellows of fresh eggs, add to this a suitable portion of a diluent, tube, and coagulate at a low temperature in an inspissator. In practice, the cultures obtained are far from uniform, and subsequent observers have sought to improve the cultural qualities of the medium by the addition of various substances, such as glycerine, amino-acids, extracts of animal tissues, etc.

Perhaps the chief difficulty with the original proposal, however, lies in the fact that the temperature of coagulation is unreliable from the point of view of sterilization. Unless the eggs are perfectly fresh and handled with every precaution, the preparations break down sooner or later, and these conditions are troublesome or actually difficult to secure, depending on the surrounding circumstances. Hence, it has become customary to carry out the coagulation as originally recommended, but then to finish the medium by sterilization at a higher temperature. With care this can be accomplished either in the Arnold sterilizer at 98° to 100°C. or in the autoclave at pressures up to fifteen pounds. The latter procedure gives sterile preparations very uniformly, even though little care has been used in the selection and manipulation of the eggs.

Since there is reason to believe that the use of higher temperatures may really injure the cultural qualities of the medium, and since the various additions have not always been subjected to careful comparative tests, we have found it advisable to make a somewhat exhaustive study of these methods. It seems not unlikely that the results may be useful to others who have occasion to cultivate the tubercle bacillus or other acid-fast bacilli. We will consider the temperature question first and secondly the results of adding various substances to the egg.

GENERAL METHODS

The eggs were obtained as fresh as possible and were placed in a disinfectant (creolin) for five minutes, in order to sterilize the shells. Then, before breaking open the egg, it was dipped into boiling water to remove any disinfectant which might adhere to the shell. The egg was broken and the contents emptied into a sterile two-litre flask, containing many sterile glass beads. After adding the desired amount of the diluent, the whole was shaken until the egg and diluent were thoroughly mixed. Then the mixture was tubed and sterilized according to the method chosen. The control tubes used in all the experiments consisted of the original Dorset's egg medium (coagulated and sterilized in the inspissator at 76°C. for a period of two hours on each of three successive days).

The source of the tubercle bacillus was fresh sputum. This was digested with 3 per cent NaOH, for one-half to two hours in the 37°C. water bath. After complete digestion, the NaOH was neutralized with 6 per cent HCl, the whole was centrifugated, and the sediment inoculated upon the surface of the egg medium. Three tubes of the modified medium under consideration in the experiment and three control tubes by the original method were inoculated with each sputum. Frequent observations were made, extending over a period of two months, before the tubes were discarded and the experiment closed.

The method of sterilizing the egg medium by autoclave is as follows: The sterilizer door is closed and permitted to stand for ten to fifteen minutes, until it is thoroughly heated by steaming. Then the steam is shut off and the outlet valve closed. The door is opened and the slanted egg tubes are placed in the sterilizer as quickly and carefully as possible, so that the cotton plugs are not touched by the egg. The door is closed and the steam turned on, and the pressure brought slowly up to 15 pounds for thirty minutes. By this method there is not so high a temperature as in regular sterilization by the autoclave, because the air which enters when placing the egg tubes in the heated sterilizer is not removed, but the temperature is sufficient to permit of sterilization if the previous preparation of the medium is carried out with due precaution.

The results of the work are shown in table 1. In the first experiment, medium made with the autoclave is compared with that by the original method. In each instance the growth obtained on the tubes made by the original method was the better. The visible difference between the

two preparations was that the medium which had been treated in the autoclave was relatively hard and dry. It was thought possible to equalize this to a considerable extent by adding more water to the medium before coagulation. This proved to be the case, but the cultural qualities were not increased thereby. This result also is recorded in table 1.

In table 2 the comparison is made between the results obtained when the medium was treated in the Arnold sterilizer and in the autoclave.

TABLE 1

The results of growth of tubercle bacilli on inspissated as compared with autoclaved egg medium

NUMBER OF CULTURE	TUBERCLE BACILLI IN SPUTUM	H_2O	METHOD OF STERILIZATION	DEGREE OF GROWTH	REMARKS
		cc.			
34	++++	25	Inspissator	Good	Best growth
		30	Autoclave	Fair	
36	++++	25	Inspissator	Good	Best growth
		50	Autoclave	Fair	
33	++++	25	Inspissator	Good	
		25	Autoclave	Fair	
		40	Autoclave	Fair	
32	+++	25	Inspissator	Good	Best growth
		50	Autoclave	Fair	
		30	Autoclave	Fair	
		40	Autoclave	Fair	
37	++++	25	Inspissator	Good	
		30	Autoclave	Fair	
53	+	25	Inspissator	Good	
		50	Autoclave	Fair	
51	+	25	Inspissator	Good	
		25	Inspissator	Good	
		50	Autoclave	Fair	

Varying quantities of water were again introduced. In some instances bouillon was substituted for the water. This is shown in the table also. In general there was little difference between the two series and growth was inferior in each instance to the controls made entirely in the inspissator.

Results similar to those recorded in tables 1 and 2 were obtained repeatedly, and there seems to be no question that in the preparation of egg medium the temperature should be kept as low as possible.

TABLE 2

Comparing egg medium sterilized in the autoclave with that treated in the Arnold sterilizer

NUMBER OF CULTURE	TUBERCLE BACILLI IN SPUTUM	H_2O ADDED	BOUILLON ADDED	REACTION OF BOUILLON		METHOD OF STERILIZATION	DEGREE OF GROWTH	REMARKS
				pH	Phenol			
		cc.	*cc.*					
10	++++	30				Autoclave	Fair	No difference
		50				Autoclave	Fair	
		25				Arnold	Fair	
11	++++	25				Autoclave	Fair	No difference
		25				Arnold	Fair	
26	++++		50	6.4	1.5	Autoclave	Poor	
			50	7.8	0	Arnold	Good	
12	+++	25				Arnold	Fair	No difference
		30				Arnold	Fair	
		30				Autoclave	Fair	
14	++++	25				Autoclave	Fair	No difference
		30				Autoclave	Fair	
		25				Arnold	Fair	
		30				Arnold	Fair	
		35				Arnold	Fair	
8	+++	30				Arnold	Good	No difference
		40				Arnold	Good	
7	+++	30				Arnold	Fair	Better growth, more moisture
		50				Arnold	Good	
25	+++		30	6.4	1.5+	Autoclave	Good	No difference
			50	7.8	0	Arnold	Good	
19	++++		30	6.4	1.5+	Arnold	Good	No difference
			50	6.4	1.5+	Arnold	Good	Better growth than last 2 tubes
			50	6.4	1.5+	Autoclave	Good	
			40	7.8	0	Arnold	Fair	No difference
			50	7.8	0	Autoclave	Fair	
22	+++		40	7.8	0	Autoclave	Good	No difference
			50	6.4	1.5+	Arnold	Good	
20	++		50	6.4	1.5+	Arnold	Good	Best growth, more moisture. No difference
			50	6.4	1.5+	Autoclave	Fair	
			30	6.4	1.5+	Autoclave	Fair	
21	+++		30	7.8	0	Arnold	Fair	
23	+++		40	6.4	1.5+	Arnold	Fair	
37	+++		30	6.4	1.5+	Autoclave	Good	More moisture
			30	6.4	1.5+	Arnold	Fair	
13	+++	30				Arnold	Good	No difference
		25				Autoclave	Good	
		40				Arnold	Good	

We have also repeatedly tried to elicit a difference between water, normal salt solution and plain bouillon as diluting fluid but have never been able to draw any distinction.

The experiments which concern the addition of various substances to the medium follow. No results with glycerine, which has been one of the common additions, are presented. It has been the regular experience of this laboratory that glycerine added to the egg medium is inhibitory when the bovine type of bacillus is to be cultivated, and that the growth of the human type is not increased by it. This refers only to the first and other early generations of cultures.

Experiment 3: To determine the results of growth of the tubercle bacillus on egg medium which contained yeast extract in place of water: The preparation of the yeast extract was according to Thjotta and Avery (*J. Exper. Med., xxxiv, no. 1*). Fifty grams of yeast were emulsified in 200 cc. of distilled water and the suspension was adjusted to pH 4.6, boiled over a flame for ten minutes and then the clear supernatant fluid was collected and tested for sterility. Before adding to the egg media, it was adjusted to various reactions (pH 6.0 to pH 8.0). The results of the several different cultivations show that there is no difference in the growth of the tubercle bacillus as compared with the controls.

When primary cultures of the tubercle bacillus are made from the guinea pig it is common experience that the cultures from the caseous lymph nodes and from the spleen grow most consistently. With this in mind the following experiment was carried out:

The spleens of normal guinea pigs were removed aseptically, ground in test tubes, and rubbed on the surface of the egg medium before inoculation. The result as shown in table 3 failed to develop any advantage for this addition.

In table 4 are presented results confirming the observations of Lyall, who showed that the addition of liver infusion improved the cultural qualities of the egg medium (Lyall, *Am. Rev. Tuberc., 1921, v, 899*).

Table 5 shows that the addition of beef bile does not promote growth.

The results in table 6 show that the fish infusion had a marked inhibitory action upon the growth of the tubercle bacillus, which was overcome by the microörganism and the final result was nearly equal to the control.

The infusion was prepared as follows: Fish (halibut) that was bought fresh at the market was finely chopped and water added. It was steamed for three hours in the autoclave and then strained through cheesecloth and placed in flasks. It was steamed on successive days for sterilization.

TABLE 3

To determine the influence of ground guinea pig spleen

NUMBER OF CULTURE	TUBERCLE BACILLI IN SPUTUM	DEGREE OF GROWTH		REMARKS
		Guinea pig spleen	Control	
36	+++	Fair	Fair	
57	++++	Good	Good	
97	+++	Fair	Good	
98	+++	Fair	Fair	
99	++++	Fair	Good	Better growth in controls
100	++++	Good	Good	
101	++++	Fair	Good	Better growth in controls
103	++++	Fair	Good	Controls slightly better
105	+++	Good	Good	

TABLE 4

To determine the influence of liver infusion

NUMBER OF CULTURE	TUBERCLE BACILLI IN SPUTUM	LIVER INFUSION		CONTROLS	
		Number of days before visible growth	Degree of growth	Number of days before visible growth	Degree of growth
146	++++	8	Excellent	15	Good
148	++	10	Excellent	16	Good
161	+++	15	Good	20	Good
158	++	12	Excellent	15	Good
157	++++	10	Good	18	Fair
159	+++	18	Excellent	20	Good
151	++++	12	Excellent	20	Good
155	++		Excellent		Good
153	+		Good		Fair
156	+++		Excellent		Good
154	++++		Good		Fair

TABLE 5

To determine the influence of bile on the growth

NUMBER OF CULTURE	TUBERCLE BACILLI IN SPUTUM	DEGREE OF GROWTH		REMARKS
		Bile	Control	
128	++++	Good	Good	
123	++	Fair	Fair	
126	++++	Good	Good	
127	++++	Fair	Good	Control slightly better growth

The results of a few observations presented in table 7 show that potato infusion has no favoring influence on the growth of the tubercle bacillus when it is added to egg medium.

The interest, which has of late been manifested in the pigments of animal and vegetable origin, led us to try the properties of a medium prepared from brown-shelled eggs, as contrasted with that made from those with white shells. The medium from the former is very deep

TABLE 6

The influence of fish infusion

NUMBER OF CULTURE	TUBERCLE BACILLI IN SPUTUM	DEGREE OF GROWTH			
		Fish media		Control	
		30 days	2 months	30 days	2 months
77	++++	Very poor	Fair	Fair	Good
78	+	Very poor	Good	Fair	Good

TABLE 7

To determine the influence of potato infusion

NUMBER OF CULTURE	TUBERCLE BACILLI IN SPUTUM	DEGREE OF GROWTH	
		Potato	Control
141	++	Good	Good
136	+++	Good	Fair
134	++++	Good	Good

TABLE 8

NUMBER OF CULTURE	TUBERCLE BACILLI IN SPUTUM	DEGREE OF GROWTH	
		Yellow	White
60	+++	Good	Good
61	++	Good	Good
62	++++	Good	Good
58	++++	Good	Good

yellow while that from the latter is almost white. The test, as shown in table 8, failed to reveal any difference.

It has at various times been suggested that the amino-acids as a group were especially good nutrients for the tubercle bacillus. Our results above presented on the effect of adding plain bouillon, which has as a basic constituent a considerable amount of commercial peptone (doubtless containing a variable proportion of free amino-acids), would

indicate that this was a general view of limited significance. There are on the market other preparations, probably rather completely hydrolized proteins, which contain a much higher percentage of free amino-acids. Four of these, marketed by the Arlington Chemical Company as "Aminoids" from beef, and from casein, have been available to us and have been included in this study. They are designated by

TABLE 9

To determine the influence of beef aminoids

NUMBER OF CULTURE	LOT 831	LOT 825	CONTROLS	REMARKS
130	Negative	Fair	Fair	
113		Good	Fair	Controls slightly inferior to 825 in growth
114	Negative	Good	Fair	
115	Negative	Good	Fair	
116	Negative	Fair	Good	
117	Negative	Poor	Good	
118	Negative	Negative	Good	
119	Negative	Poor	Good	
120	Negative	Fair	Good	
121		Poor	Good	
124	Negative	Fair	Fair	
125	Poor (few minute colonies)	Good	Good	
126	Negative	Good	Good	
127	Poor (few minute colonies)		Good	
132	Negative		Fair	
141		pH 8.0 to 6.4 fair	Good	
134		pH 7.0 good	Good	
136		pH 7.8 fair	Good	
139	pH 7.8 negative		Good	
142	pH 5.2 to 7.0		Good	
143	pH 7.0 to 7.8 negative		Fair	

our own numbers, and accompanied by certain analytical figures furnished by the manufacturer, which we have not verified, as follows:

No. 831: Aminoids from beef; amino-acid nitrogen is 60 per cent of total nitrogen.

No. 825: Aminoids from beef; biuret-free; total N 11.98 per cent, amino N 8.9 per cent.

No. 820: Aminoids from casein; amino N is 50 per cent of total N.

No. 828: Aminoids from casein; biuret-free; not further analyzed.

The results are presented in tables 9 and 10. It appears that the products numbered 820 and 831, which are considered to be but partially hydrolized, are actually inhibitory to the growth of the tubercle bacillus under the conditions of our experiments. Of the biuret-free preparations, numbers 825 and 828, that derived from casein, consistently improved the growth, while the preparation from beef seemed indifferent.

TABLE 10

To determine the influence of casein aminoids

NUMBER OF CULTURE	LOT NO. 820	LOT NO. 828	CONTROLS
130	Negative	Good	Fair
113		Excellent	Good
131		Good	Fair
114		Fair	Fair
115		Excellent	Fair
116	Negative	Excellent	Good
117	Fair	Good	Good
118		Very good	Good
119	Fair	Excellent	Good
120	Good	Excellent	Good
121	Good	Excellent	Good
124	Negative	Good	Fair
125	Fair	Excellent	Good
126		Excellent	Good
127		Excellent	Good
132	Poor		Fair
134		pH 7.8 excellent	Good
135		pH 7.8 excellent	Good
136		pH 7.0 good	Good
142		pH 5.2 excellent	Good
143		pH 5.2 good	Good
145		pH 5.2 to 6.4 good	Good
140		pH 6.4 excellent	Good
144	pH 6.4 to 7.8		Fair

Evidently there is no general rule to be stated for all preparations in which amino-acids are present as important constituents. So far as we know the only suggestion that substances of this type might actually be inhibitory to bacterial growth is found in a recent paper by Swoboda (*J. Biol. Chem., 1922, lii, 91*), who finds that certain amino-acids may either stimulate or retard the growth of yeast, depending on the presence of other substances.

In the experiments here given the "Aminoids" were added in the usual amount of diluting fluid to make a concentration of 5 per cent in

the finished medium. This is obviously much higher than the usual concentration of peptone in culture media and this may account for the unexpected result, which does not, however, lose its interest on that account.

CONCLUSIONS

1. In the preparation of Dorset's egg medium the original method should be followed, in so far as that the coagulation and sterilization should be carried out at 76°C. Higher temperatures injure the nutritive qualities of the medium for the tubercle bacillus.

2. Normal salt solution, plain bouillon, beef bile and potato infusion used as diluents for the egg, are not superior to water.

3. Liver infusion (Lyall) used as a diluent gives rise to decidedly superior growths.

4. "Biuret-free aminoids from casein" (Arlington), when added to the egg medium in proportion of 5 per cent of the finished preparation, gives growths superior to those secured with the original.

5. The other "Aminoid" preparations (also Arlington) those from casein or from beef, used in the same way, either fail to increase the growth of the tubercle bacillus or actually inhibit growth completely.

6. Normal guinea pig spleen, when rubbed on the surface of the egg medium, does not promote the growth of the tubercle bacillus.

STUDIES ON THE BACTERIAL FLORA OF THE SPUTUM FROM CASES OF TUBERCULOSIS AND OTHER CHRONIC RESPIRATORY INFECTIONS*

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The question of the significance of mixed infection in tuberculosis has been the subject of much debate in times past. It would serve no useful purpose to revive the argument at this time. Suffice to say that those whose views on the pathology of the disease are much under the influence of the results of animal experimentation are probably quite in accord to-day in so far as they recognize that the tubercle bacillus is entirely competent, unaided by other bacteria, to produce all of the characteristic phenomena of the disease; fever, caseous consolidation, and cavitation being those about which most question has arisen in the past. It is at least equally apparent that secondary infection when it exists may very greatly complicate the course of the disease, either clinically or in the anatomical sense. The exact significance of these complications may doubtless be determining in time, and the subject is worthy of further study at any time that precise methods of observation can be brought to bear upon it.

Problems of even greater importance, perhaps, are constantly arising in connection with the differential recognition of chronic non-tuberculous infections of the respiratory tract. Success in this field as in the other must depend on the continued, patient and discriminating application of the best bacteriological methods in association with careful clinical observation. The bacteriological work has in the past been especially unsatisfying.

We have, up to now concerned ourselves only with the results of the examination of the sputum. Review of the literature shows three distinct methods have been relied on, namely:

(1) Microscopic examination unaided by cultivations.
(2) Cultivation from the whole sputum as collected.
(3) Cultivation from the sputum after washing away the fluid portions, and the loosely attached bacteria associated with the more solid and insoluble parts.

The first two methods whether used separately or together are subject

* From the Eagleville Hospital, and the Henry Phipps Institute of the University of Pennsylvania, Philadelphia.

to obvious shortcomings which are well understood. The third method, that is the study of the washed sputum, has always seemed more likely to give truly representative results, and is the one whose merits we have been particularly concerned to examine. This method should in practice, always be complemented by microscopic and cultural examination of the unwashed sample.

In reviewing the literature pertaining to the technique of washing the sputum, we will find that there are two principal methods for washing the sputum, namely: (1) The "Koch-Kitasato" method, and (2) the mechanical method. The other methods of washing sputum are modifications of these two.

After having used the Kitasato[1] method of washing the sputum, we felt that it was not satisfactory for routine purposes. Then we constructed Harvey's[2] device for the mechanical washing of sputum and followed his directions as closely as possible, but had very little success with it, especially in the manipulation of the apparatus.

We then endeavored to devise an apparatus which might overcome the difficulties we had encountered, and yet keep the Harvey principle of rotating the sputum by a continuous flow of sterile water. The apparatus for washing which we developed consists of a two-liter flask of sterile water emptying by a siphon into a 50 cc. Erlenmeyer flask, through a tube of special design. The reservoir flask is placed several feet above the wash flask, proper union being effected by rubber tubing. The bent tube in the flask is so shaped and so placed that it ejects the water around the sides of the flask, and by this means a rotating stream is produced. The water passes off through the outlet as waste. The flask is adjusted so that the sputum particle is in the central portion of the stream of water and is, thereby, continuously agitated. The sputum particle may be washed for any desired period by constantly substituting a two-liter flask of sterile water as each preceding flask is emptied.

If the bacteriological examination of sputum is to be satisfactory, three main precautions must be taken. First, the sputum must be collected properly. The patient should gargle and wash his mouth thoroughly with sterile salt solution before expectorating into a sterile receptacle. This keeps down the number of mouth bacteria in the sample. In the study of tuberculosis, asthma, and bronchitis, it is necessary to obtain a representative sample of the sputum and not a specimen secreted from the nasopharyngeal region.

Second, the sputum must be studied immediately after it has been obtained. It has been shown by several investigators that B. influenza and the pneumococcus are not to be recovered from the sputum more than a short time after expectoration. Likewise, if the sample stands about the mouth bacteria tend to multiply, and the whole numerical relationship of the bacteria of the true sample also changes from hour to hour.

Third, the sputum must be thoroughly washed. The washing of the sputum is regarded as complete when cultures of the wash water on

plated blood agar and in plain bouillon remain sterile. If growth from the wash water is obtained it means that the loosely attached bacteria have not been entirely removed.

The routine method which we follow for the study of sputum is (1) to study stained smears of the direct sputum culture; (2) to make a direct culture from the unwashed sputum on blood agar plates and Sabaroud's agar, the purpose of the two procedures being to obtain a general idea of the micro-organisms present; (3) the washed sputum particle is so divided that one section may be inoculated on the surface of a blood agar plate, second section is inoculated in a blood bouillon tube from which blood agar plates are later poured according to Brown's technique[3] for the study of deep colonies of streptococcus, and the third section is planted on Sabaroud's Agar in order to obtain any yeasts or molds which may be present. In the case of suspected tuberculous sputum, a stained smear is examined for the presence of the tubercle bacillus.

Our studies were carried out during the early months of 1921, and the recent months of 1922. The specimens were obtained from 69 clinically positive tuberculous cases; 48 asthma cases considered to be of bacterial origin, and 16 other chronic non-tuberculous cases.

The study of 69 sputa of the tuberculous cases during the two years, showed that 28 per cent. of the sputa could be washed free of all bacteria except the tubercle bacillus, while the 48 sputa obtained from asthma cases and 16 sputa obtained from chronic non-tuberculous cases, always contained one or more residual types.

The tuberculous sputa which were not washed free from secondary invaders were studied from the point of view of the different types of bacteria that remained in the residue. During the early months of the year 1921, streptococcus non-hemolyticus (alpha type) were found in the greatest frequency (64 per cent.), while the hemolytic streptococci (beta type) were found in only 3 per cent. of the cases. The order of frequency of the other varieties for this period is as follows: diptheroids, staphylococci, M. catarrhalis, M. tetragenous, pneumococci, B. influenza and B. Friedlander.

During the winter of 1922, streptococcus non-hemolyticus (alpha type) was found with the greatest frequency (47 per cent.), while hemolytic streptococci were found in 18 per cent. of the cases, which is a considerable increase over the first year (1921).

During the first part of March, 1922, a number of hemorrhages occurred at one time among the patients in the Eagleville Hospital. This seemed to be associated with the increase of hemolytic streptococci. There were six cases of hemorrhage during this period of which five showed a hemolytic streptococcus in the washed sputum. The other hemorrhagic case showed a hemolytic streptococcus in the washed sputa three days later. The hemolytic streptococci were found at this time, as above stated, in 18 per cent. of the cases studied.

We then repeated the washing of the sputa from all the patients in the hospital at monthly intervals for three successive months. There was a gradual decrease of hemorrhages and a simultaneous, but slower decrease of the hemolytic streptococci, until the presence of hemorrhages were negative and the hemolytic streptococci occurred at the usual rate of frequency in such cases, namely 3 to 5 per cent.

An example of an interesting case showing the invasion of hemolytic streptococci is as follows: On January 30th, the sputum was washed free from all bacteria except the tubercle bacillus. On March 27th, the sputum was streaked with blood but the washed sputum did not show the presence of hemolytic streptococci until six days later when it was found in pure culture. On April 19th, the washing of the sputum was again repeated and the residue was washed free from every organism except the tubercle bacillus.

Molds or yeast were never found in the washed sputum of the tuberculous cases studied.

The frequency of the various types of organisms which remained in the washed sputa of the 48 asthma cases was as follows: Streptococcus non-hemolyticus occurred in 54 per cent. of the cases, while the hemolytic streptococcus (Beta Type) occurred in 6 per cent. of the cases. B. Friedlander, the next of frequency, occurred in 16 per cent. of the cases, while gram negative cocci, B. influenza, staphylococci, pneumococci, and diptheroids occurred in the order mentioned.

The frequency of the different types of bacteria that remained in the washed sputum of the 16 chronic non-tuberculous cases shows that streptococcus non-hemolyticus occurred in 68 per cent. of the cases and B. influenza in 62 per cent. of the cases, while the hemolytic streptococcus occurred in 12 per cent. of the cases and the other types of organisms in various order of frequency. One case showed the development on Sabaroud's Agar of a mould belonging to the aspergillus group. This case could not be secured for repeated examination.

In conclusion:

The washing of the sputum as we have used it seems adapted to continuous use as a routine method.

The residue after washing is fairly constant as to its bacterial content. Particularly yeasts, molds and the common bacteria of the air are practically eliminated from consideration. Whether significant bacteria are also washed away must for the present remain a matter of doubt.

The residual bacteria in tuberculosis, bacterial asthma and other chronic infections of the respiratory tract differ more in their percentage distribution within the clinical groups than in kind.

The freedom of almost one-third of the tuberculous cases from any other bacteria than the tubercle bacillus, the association of an increase of hemolytic streptococcus with epidemic hemorrhage in a group of tuberculosis cases and the higher percentage of influenza bacilli in the chronic infections other than tuberculosis and asthma during recent

months are perhaps the more significant of our observations with the method.

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SPECIFIC PURIFICATION OF ANTI-TUBERCULOSIS SERUM*

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The fact that immune bodies can be precipitated from anti-pneumococcus serum by the addition thereto of an autolyzed extract of the specific antigen, has been demonstrated by Gay and Chickering. The work of Weinstein, Kosaki and Huntoon has corroborated the findings of Gay and Chickering.

An attempt was made by us to determine whether the immune bodies present in an anti-tuberculosis serum could be concentrated and purified by the addition of its specific antigen.

Method: An anti-tuberculosis serum was prepared by injecting a goat at irregular periods of time, with a living, avirulent culture of a strain of bovine bacillus. This serum, in the presence of its antigen, showed complement fixation in a quantity as small as .0001 cc. A number of different methods were used to prepare the precipitinogen.

A. Alcoholic extract of B. tuberculosis was prepared by extracting dry tubercle bacilli in a Soxhlet with boiling alcohol until all of the antigenic substance was removed.

B. Bacillary emulsions of B. tuberculosis were prepared by grinding the weighed mass of tubercle bacilli in an agate mortar for a long time and gradually adding salt solution, in order to bring it to the desired concentration.

C. Autolyzed extract of B. tuberculosis was prepared in the same manner as that used by Chickering in preparing his pneumococcus precipitinogen. Unlike the pneumococcus, the tubercle bacillus goes into solution but slightly, yielding a distinctly opalescent fluid.

D. A salt solution extract was prepared by boiling tubercle bacilli in salt solution for 15 minutes, centrifuging and using the clear fluid.

Removal of Immune Bodies: The immune bodies were removed by adding the antigen to the diluted serum, and, in the case of the alcoholic antigen, the diluted antigen was added to the serum. The mixture was then incubated for 2-4 hours, and in some experiments for 18 hours. No

* From the Henry Phipps Institute of the University of Pennsylvania, Philadelphia.

difference in results was noted when the antigen was added in one dose or in repeated smaller doses.

The addition of the antigen to the immune serum resulted in the production of a precipitate, the volume of the precipitate varying with the antigen used and being most marked when the alcoholic extract was employed.

The supernatant fluid was removed by centrifuging until clear, and the precipitate was washed 3-4 times with salt solution. Unless otherwise stated, the results given were obtained by the addition of alcoholic extract to the immune serum. It was soon found that the addition of the amount of antigen which theoretically should bring down all of the immune bodies, brought down but 60 per cent. of them, and it was not until 66 per cent. more than the theoretical amount of antigen had been added that all of the immune bodies were removed.

To determine the removal of immune bodies from the supernatant fluid, use was made of the complement fixation reaction, since the results obtained by means of agglutination and precipitation reactions are indefinite and not so sensitive as those obtained by means of complement fixation. No attempt was made in this work to determine the absence or presence of immune bodies having a protective value.

The determination of the presence or absence of immune bodies was made by adding two units of antigen and complement to the supernatant fluid, incubating for 2 hours, then adding a hemolytic system and incubating for 30 minutes more. The result was then read. The results obtained indicated that all of the complement fixing bodies could be removed by the addition of a sufficient quantity of antigen. In the course of this work we noted the fact that free antigen and complement fixing bodies could be demonstrated in an uncombined state in the supernatant fluid. This fact has also been noted by Linossier and Lemoine, by Eisenberg, and by Weil in reference to the presence of free precipitin and precipitinogen in a mixture of the two.

The removal of complement fixing bodies can be carried out also by using a bacillary emulsion or a bacillary extract prepared by boiling in salt solution, or by an autolyzed extract prepared according to the method of Chickering.

Specificity of Reaction: From our previous results in a study of complement fixation in tuberculosis, we found that with the exception of the B. lepra Duval and B. kedrowski, none of the acid fast bacteria at our disposal fixed an immune tuberculosis serum. In order to test further the question of the specific function of the antigen, we attempted to remove the immune bodies from the serum by the addition of a bacillary emulsion of B. rabinovitch (myc. lacticola phlei) to the immune serum which did not form a precipitate, and no removal of immune bodies from the supernatant fluid was demonstrable.

The addition of 95 per cent. alcohol in amount equal to the amount

of alcohol present in the alcoholic extract of the tubercle bacillus, did not remove any of the complement fixing bodies.

Dissociation of the Precipitate: The precipitate was washed in 3-4 changes of salt solution and the washings tested for the presence of free immune bodies. The first washing always showed a trace, but subsequent washings were generally free from immune bodies.

The liquid was carefully removed from the precipitate which was then treated in different ways to break up the antigen-antibody complex. For the purpose of dissociation, we made use of salt solution, distilled water, freezing and thawing, dialysis through a *collodion* sac, filtering through a Mandler filter, heating at 70° for 30-45 minutes, and weak sodium carbonate solution. The method consisted of adding to the precipitate, the various substances used as extractives; incubating for 2 to 4 hours of 42°C; centrifuging and testing the supernatant fluid for the presence of free antigen by the addition of free immune serum, and for the presence of free immune bodies by the addition of fresh antigen; adding complement to the tubes; incubating for 2 hours; adding a hemolytic system; and reading result within 30 minutes and again the next morning. Extracting with water or with salt solution yielded but 10 per cent. of the immune bodies, while .1 per cent. sodium carbonate yielded a 15 per cent. return by this method. Dialyzing the salt solution extract did not give a better yield than the undialyzed control. Freezing and thawing the extract in salt solution gave but a 6 per cent. yield of antibodies. Filtering the salt solution extract through a Mandler filter and adding charcoal to the extract removed both antigen and antibody from the extract. Heating to 70°C shows a marked destruction of the immune bodies and a liberation of the antigen.

By extracting the precipitate for a week or longer in dilute sodium carbonate in the ice box, we have succeeded in recovering 50 per cent. of the immune bodies in a free state. Neutralization of sodium carbonate extract with HCl does not cause a drop in this titre of the immune bodies. It is interesting to note in this connection that Weinstein, using an antiformin extract of B. typhosus and typhoid immune serum as the precipitin, succeeded in extracting about 5 per cent. of the agglutinins, 50 per cent. of the bactericidal bodies, and 10 per cent. of the complement fixing bodies.

Active Immunization with Precipitate: Rabbits immunized with the precipitate containing the antigen and antibody show a rapid production of immune bodies having a high titre.

SUMMARY

1. Immune bodies possessing the properties of amboceptor can be removed from their menstrum by means of their specific antigen.

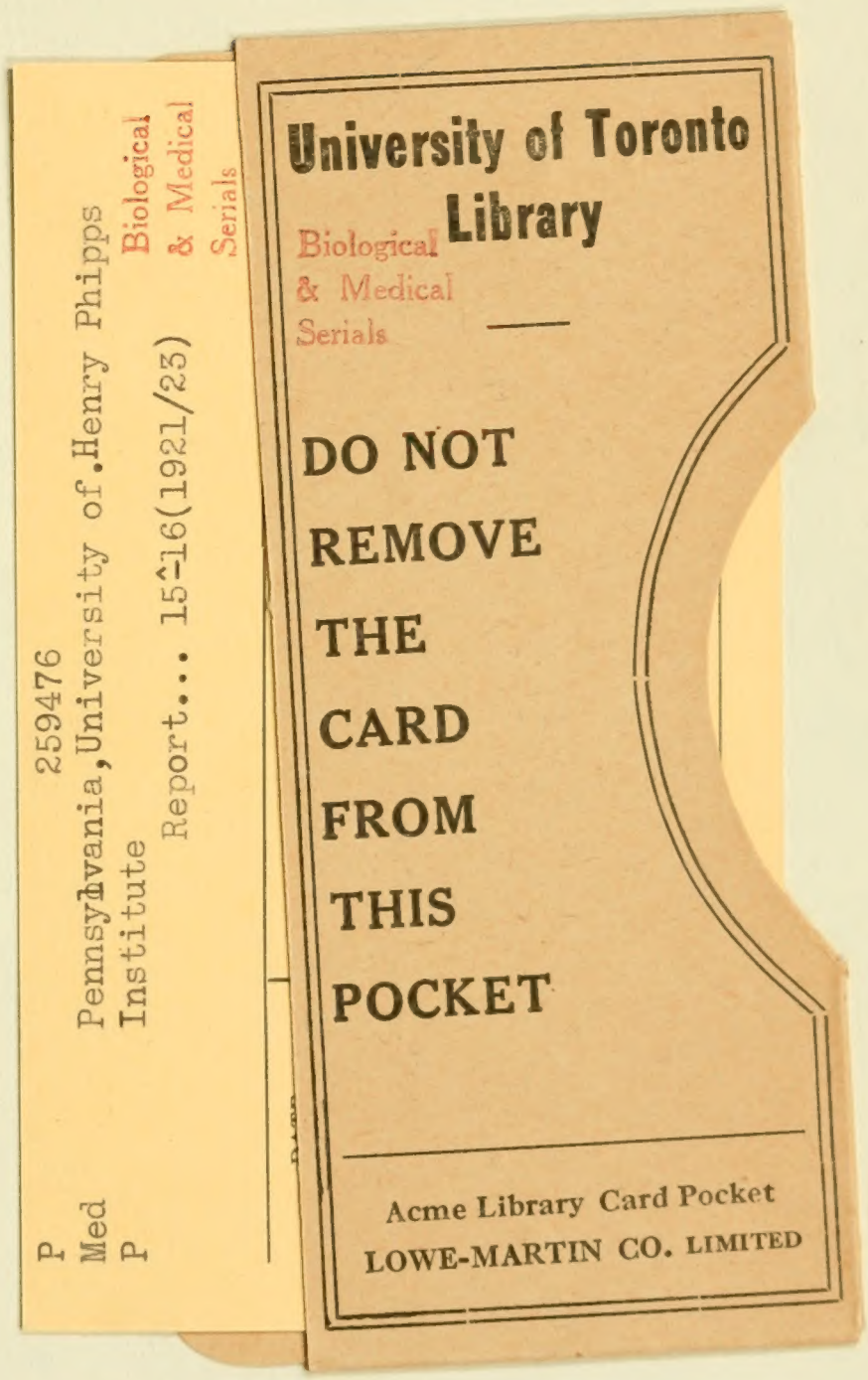
2. The degree of completion of the removal of the immune bodies is

a quantitative one and is specific, and can be carried out without regard to the method of preparing the antigen.

3. Antigen and antibody can exist in an uncombined state.

4. Precipitate can be dissociated by treating with salt solution, water or a weak alkali, the latter yielding the best results especially after prolonged extraction.

5. Precipitate can produce active immunity.

6. Precipitate cannot be completely dissociated.

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